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Application of UV-Induced Unscheduled DNA-Synthesis Measurements in Human Genotoxicological Risk Assessment

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1. Introduction

1.1 Environmental endogenous DNA damages

Cancer development is a long-term, multistep process with a complex interplay between genes and environment. The magnitude of environmental effects depends on the presence or absence of genetic susceptibility of the subjects to certain cancer types. Molecular epidemiological studies in cancer have proved that besides target cell genetic instability, the presence of triggering environmental exposure is critical in cancer development [Albertini & Hayes 1997, Newby & Howard 2005]. The biomarker responses, exposure character and the route of exposure of different environmental factors (chemicals, physical agents and biological agents) are also important in causing tumors especially in the cases of occupational cancer [Ward 1995]. The EPA Guidelines for carcinogen Risk Assessment [EPA 2005] is based on the mode of action of chemicals, such as interaction with DNA, cytotoxicity, or binding to the receptors modifying signal pathways. There are several natural compounds – so called chemopreventive agents- which are able to modify the genotoxic or mutagenic response (Ames 1983) in different organisms. These vitamins, antioxidants, phytochemicals, micro nutrients are available on the market without knowing their mode of action. Mutagenesis caused by environmental chemicals or physical agents can be prevented by protection of the cell's DNA replication, increasing the repair capacity or delaying cell replication to allow enough time to make a complete repair of damaged cells. Antioxidants are able to protect the cells from oxidative stress, and stimulate the phase I reactions including oxidation, reduction, and hydrolysis of xenobiotics by the monoxigenase detoxicating key enzymes, such as CYP450 [Xu et al. 1996, Poulsen & Loft 1998]. These changes increase the polarity of these molecules and help to conjugate them in phase II to glucuronic acid, acetic acid and sulfuric acid which are the physiological ways to eliminate active metabolites that are genotoxic to the target cells. The best studied crucial early event in carcinogenesis is chromosomal aberration, including microsatellite instability, abnormal number of chromosomes (aneuploidy), gene amplification or the loss of heterozygosity of tumor suppressor genes. By reducing chromosomal mutation via chemoprevention, the cell may be able to survive the genotoxic effects without any permanent damage, or it is able to go through the physiological pathway of apoptosis, without mutation occurring in the P53 gene [Lowe & Lin 2000].

1.2 The role of DNA repair in gene-environmental interactions

The measurement of UV-induced DNA repair is recommended in the risk assessment of environmental exposure to harmful chemicals (Reg. 440/2008/EC). Data obtained on prokaryota organisms suggest that exposure to chemicals as e.g. free oxygen radicals can interact with UV-induced DNA repair mechanisms (Chandor-Proust et al, 2008). Among the repair mechanisms existing in higher eukaryota, base excision repair (BER) seems to be the main mechanism involved in the removal of lesions produced by alkylation, deamination or oxidation (Rastogi et al, 2010). Orelli et al. (2009) demonstrated recently that nucleotide excision repair (NER) also plays an important role in the development of cisplatin resistance. UV-induced DNA damages can induce the so called three prime exonuclease1 (trex1), as a response to genotoxic stress. Beside thymine dimer production, UV irradiation can also produce reactive oxygen species. Benzo(a)pyrene (BaP) and hydrogen peroxide may, similarly to UV, induce the so-called three prime exonuclease1 (trex1) involved in the repair pathways of UV-induced DNA lesions, and cells deficient in trex1 show reduced recovery from UV and BaP replication inhibition, and increased sensitivity to towards genotoxins compared to the isogenic control (Christmann et al, 2010). These data suggest that both main mechanisms can be involved in the total repair of environmental chemical-induced genotoxic stress. Such mechanisms can probably explain the observed UDS reduction in some of our groups exposed to various chemicals but not UV.

A second question is whether decreased UDS can be related to an increase in apoptotic capacity? Cells deficient in the repair of UV-induced DNA damage can be more susceptible to a G1 arrest after UV treatment than cells with normal repair capacity or those cells which have completed their DNA repair prior to movement from G1 to S phase (Geyer et al, 2000). Zampetti-Bosseler and Scott (1981) demonstrated a prolonged mitotic delay in repair deficient ataxia teleangiectasia and retinoblastoma fibroblasts after X-ray irradiation compared to normal human fibroblasts, also suggesting a general key role of cell cycle check points beside DNA repair in preservation of genome stability (Kaufman, 1995). Skin fibroblasts from derived ataxia teleangiectasia patients are also more sensitive to UV-induced mutagenesis than those taken from healthy subjects (Hannan et al, 2002), and their results suggested a relationship between cell cycle control and DNA repair pathways in human cells. Genotoxic chemicals can also delay cellular proliferation in DNA repair-deficient cell clones more significantly than in wild type cells, by interfering with DNA replication, thereby inducing DNA damage (Kyunghee et al, 2009). The recently discovered cell cycle checkpoint activation mechanisms are discussed in detail by Rastogi et al (2010). In the present study the so-called premature centromere division (PCD) was used as a cytogenetic indicator of abnormalities in cell cycle regulation (Méhes 1978, Vig, 1981, Major et al, 1999). PCD yields were increased among cytostatic drug producers, anesthesiologists using halothane, and in exposures to formaldehyde, benzene and PAHs. PCD can be involved in the pathomechanism of aneuploidy, it seems to be a possible manifestation of chromosome instability also in human chromosome breakage syndromes and it can be connected with carcinogenesis (for review, c.f. Major et al, 1999).

2. Cancer development and DNA repair

We don't know exactly what the cause of cancer is; therefore we have several mechanisms and theories to explain it. One of them is shown in Fig.1.

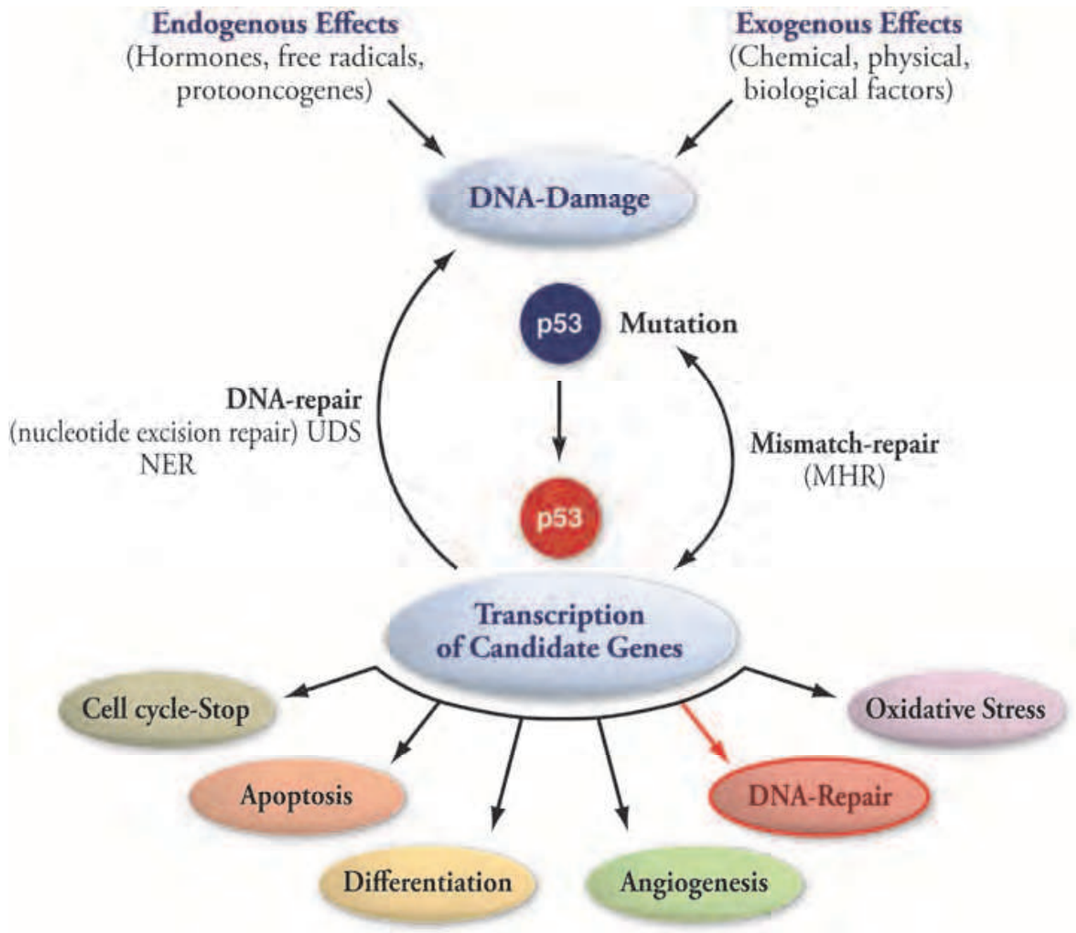

Fig. 1. Basic mechanism of cancer development

Figure 1. explains the genotoxic mechanism of cancer development, in which the P53 gene mutation is caused by DNA damage, and the consequence of this mutation leads to an inhibition of cell cycle arrest, or in differentiating cells, induces angiogenesis and inhibits the apoptotic activity of mutated cells. These changes are randomly mixed in target cells influencing clonal proliferation. The development of cancer is known to be a multistep process that is theoretically divided into initiation, promotion and progression (Fig. 2). Accumulation of mutational events necessarily leads to immortalizing the target cell. During this process the cells express several changes in phenotype. Most attractive changes are chromosomal aberrations (numerical and structural), easily detectable in cells, such as peripheral blood lymphocytes (PBL). Several epigenetic mechanisms are involved in cell initiation and promotion, eg. inhibition of DNA methyl-transferases, or DNA-repair enzymes (Ames 1989). Genotoxicity occurs when xenobiotics modify the DNA structure causing DNA damages which can lead to cytotoxicity or mutagenesis. DNA repair mechanisms are responsible for keeping the DNA in normal conformation and removing the lesions by enzymatic reactions. The damaging agents are divided into two main categories: endogenous and environmental agents. The endogenous factors are generated during normal metabolism; therefore these DNA damages are unavoidable and are related to sporadic and hereditary cancer (Valko et al. 2004, Bartkova et al. 2005). Usually the

physiological activities of DNA-repair and antioxidant systems are sufficient to keep these damages in balance, except when this machinery is already genetically altered. Although these damages are crucial in cancer development (Bardelli et al.2001), several other epigenetic events may lead to genomic instability, which initiate spontaneous chromosome breakage. Many other methods are used as biomarkers for DNA damage such as DNA strand breaks, chromosome aberrations (CA), micronucleus assay (MN), DNA-adduct, point mutation (HPRT) and epigenetic markers like DNA-methylation status, or the examination of the slow acetylation status among dye workers. These biomarkers are used in risk assessment of occupational and environmental cancer (Sorsa 1984, Forni 1987, Norppa 1997, Tompa et al. 2007) and they are important tools in analytical epidemiological studies, when intervention is necessary to avoid cancer development in the future (Hayes 1992).

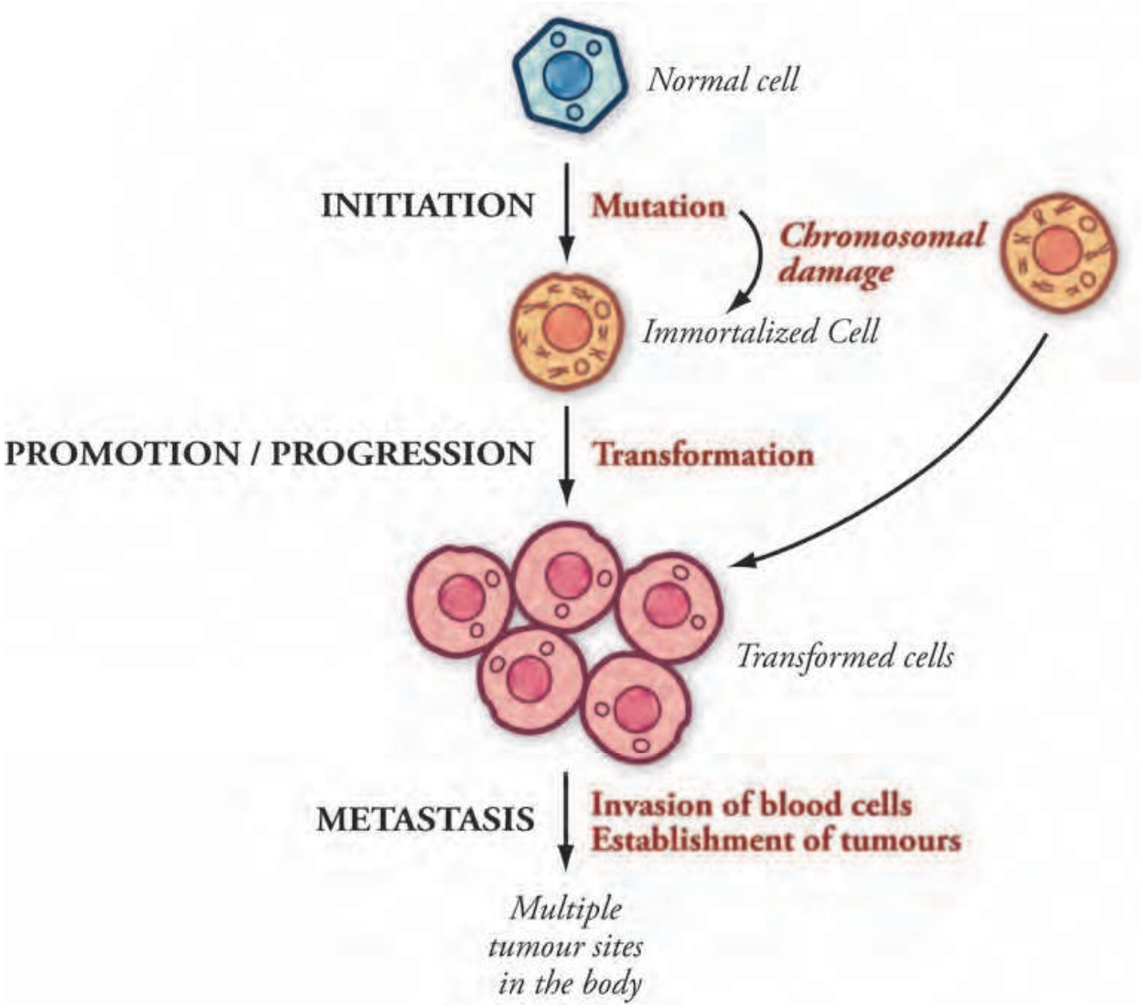

Fig. 2. Main steps of the multistep theory of cancer development: initiation, promotion and progression

In the case of high cancer risk, chemoprevention can be indicated with the help of these biomarkers. Several cohort follow up studies have shown a 2-3 fold increase in cancer risk among those individuals who have previously had a permanent high level of

chromosomal aberrations, (Bonassi 2000) compared to controls, who have low level of CAs [Nordic Study Group 1990]. Diet is able to influence the base-line mutation in DNA since folic acid and other antioxidants and selenium supplementation can prevent DNA amplification and double stranded DNA breaks (Fenech 2001, Crott et al. 2001) caused by different alkylating agents e.g. methotrexate. Several micronutrients such as zinc, magnesium, folic acid and vitamin B12 are required as a co-factor in normal DNA metabolism. Not only direct carcinogen exposure can be genotoxic, but the deficiency of these protective factors can also cause chromosomal aberrations, genetic instability and gene mutations in somatic cells which can lead to cancer. The supplementation of these chemopreventive agents (given with indication, based on the evidence of low serum levels), may give us a future perspective in anti-cancer treatment in the early stage of cancer development (Klein, Thompson, 2004). The balance of micronutrients, antioxidants and any other chemopreventive agents are regulated and kept very precisely at individually specific levels, and adopted by the optimal balance according to the functional requirements. Reactive oxygen species (ROS) do not necessarily play a negative role in cell metabolism. The white blood cells, such as neutrophils and macrophages produce a great amount of ROS during phagocytosis (Meydani et al. 1995). Unnecessary antioxidant treatment may inhibit immune surveillance and can cause immune suppression during chemoprevention. Without the measurement of antioxidant status this treatment is probably more hazardous than helpful. The presence of individual susceptibility markers of cancer development, like chromosomal mutation, DNA-repair capacity, or HPRT-point mutation must be tested parallel to the detection of antioxidant status. Chemopreventive action may be indicated on the basis of the positivity of the investigated biomarkers. The basic concept, first introduced by Brewer (1971) and Motulsky (1991), ie. genetic variations affect the adaptation to any kind of environmental agent, created the new expression “ecogenetics”, explaining the reasons for individual susceptibility. Genetic polymorphism is the variation of normal phenotypes in the population, which usually does not alter the basic function of genes, but may modify the inducibility of the synthesis of the coded protein.

When gene expression changes without DNA sequence change, it is considered as “epigenetic” carcinogenesis. These heritable changes may include the methylation of cytosine bases in the DNA, or the modifications of histone proteins (acetylation, methylation, and phosphorylation). Hypermethylation of CpG-rich promoter regions are one of the most common epigenetic changes during carcinogenesis [Ames 1985, 1993, Baylin& Ohm 2006].

In physiological conditions the mammalian genome is often methylated at the C5 position of the cytosine by DNA methyltransferases. This mechanism plays a critical role in epigenetic gene silencing. When the methylation occurs in a different position on the DNA, this process may lead to serious DNA damage without mutation. S-adenosylmethionine (SAM) is a major methyl donor in various biosynthesis processes in normal cells. It is able to donate methyl groups to the DNA without an enzymatic reaction. Methionine deficiency may cause hypomethylation of DNA, which causes higher vulnerability of DNA replication during the cell cycle. In the absence of DNA methylation, there is increased nuclear clustering of pericentric heterochromatin and extensive changes in primary chromatin structure and global levels of histone H3 methylation and acetylation also become altered. This is one of the reasons why altered methylation of DNA can decrease the mobility of chromatin structure and nuclear

organization. In general DNA methylation is important in the control of gene transcription and chromatin structure. The complexities of this process are just beginning to be elucidated in relationship to other epigenetic mechanism of cancers [Feinberg et al. 2002]. Other histone modifications, such as acetylation and phosphorylation, affecting histone methylation also appear to be highly reliant on chromatin remodeling enzymes. The chemopreventive effects of sodium selenite and benzyl thiocyanate and their inhibitory effect on methyltransferase activity was demonstrated on human cultured colon carcinoma cells (Fiala et al. 1998).

3. Reactive oxygen species (ROS) and cancer chemoprevention

All cells of every organism are continuously exposed to free radicals, or reactive oxygen species (ROS) produced by oxidation that is an integral part of physiological metabolism, and controlled by physiological antioxidant mechanisms like phase II enzymes (superoxide dismutase, catalase, glutathione peroxidase). Oxidative stress arises, when the level of ROS exceeds the cell antioxidant capacity. Generation of ROS in different individuals is roughly correlated with life span, and defines the rate of aging and age related diseases like cancer (Klaunig et al. 1998). Several cellular defense mechanisms are available to protect the cellular compartments from oxidative damages, like superoxide dismutase and catalase and vitamins E and C which function to terminate lipid chain reactions involving free radicals. Many environmental xenobiotics induce free radicals reacting with DNA, RNA, proteins and lipids, forming adducts with nucleic acids. Chemoprevention of free radical formation is one of the best scientifically established ways of cell protection against mutagenic agents. Vegetarian food and different food supplements have enough antioxidants to prevent oxidative damage of macromolecules. Consumption of mediterranean food, olive oil, fish, vegetables, citrus fruits, green tea etc. caused differences in statistical appearance of cancer types and incidences, as well as in other chronic diseases (Trichopoulou et al. 2000). All of these beneficial effects are related to the antioxidant contents of diet and the relaxed life style.

Several in vivo and in vitro studies described the beneficial effects of antioxidants like polyphenols, terpenoids or vitamins in preventing cancer development or cell transformation. Although some human studies have described failure to prevent lung cancer among smokers and miners in long-term chemoprevention trials (Omenn et al. 1996). In a smoker group the supplementation with synthetic beta-carotene even increased the incidence of lung cancer, because the high dose caused a prooxidant effect during liver metabolism (Hennekens et al. 1996). In some other human trials, selenium, vitamin E and D, cyclooxygenase-2 inhibitors, lycopen and green tea were useful in reducing prostatic cancer development among PSA positive patients, except in those individuals, who had already in situ carcinoma (Mayer et al. 2005, Klein & Thompson, 2004).

Approximately every fifth cancer case is related to chronic inflammation; therefore anti-inflammatory agents are also used in chemoprevention, especially in the case of gastrointestinal cancer. Aspirin, piroxicam, ibuprofen or the naturally occurring sulindac has been shown to lead to a total regression of colorectal adenomatous polyps in patients with familiar adenomatosis (FAP). Vitamin D is also used as a chemopreventive agent, because it increases the apoptotic pathway through the inhibition of proliferation signals at the bcl2 gene expression level, as it is shown on Fig. 3. (Weitsman et al. 2003).

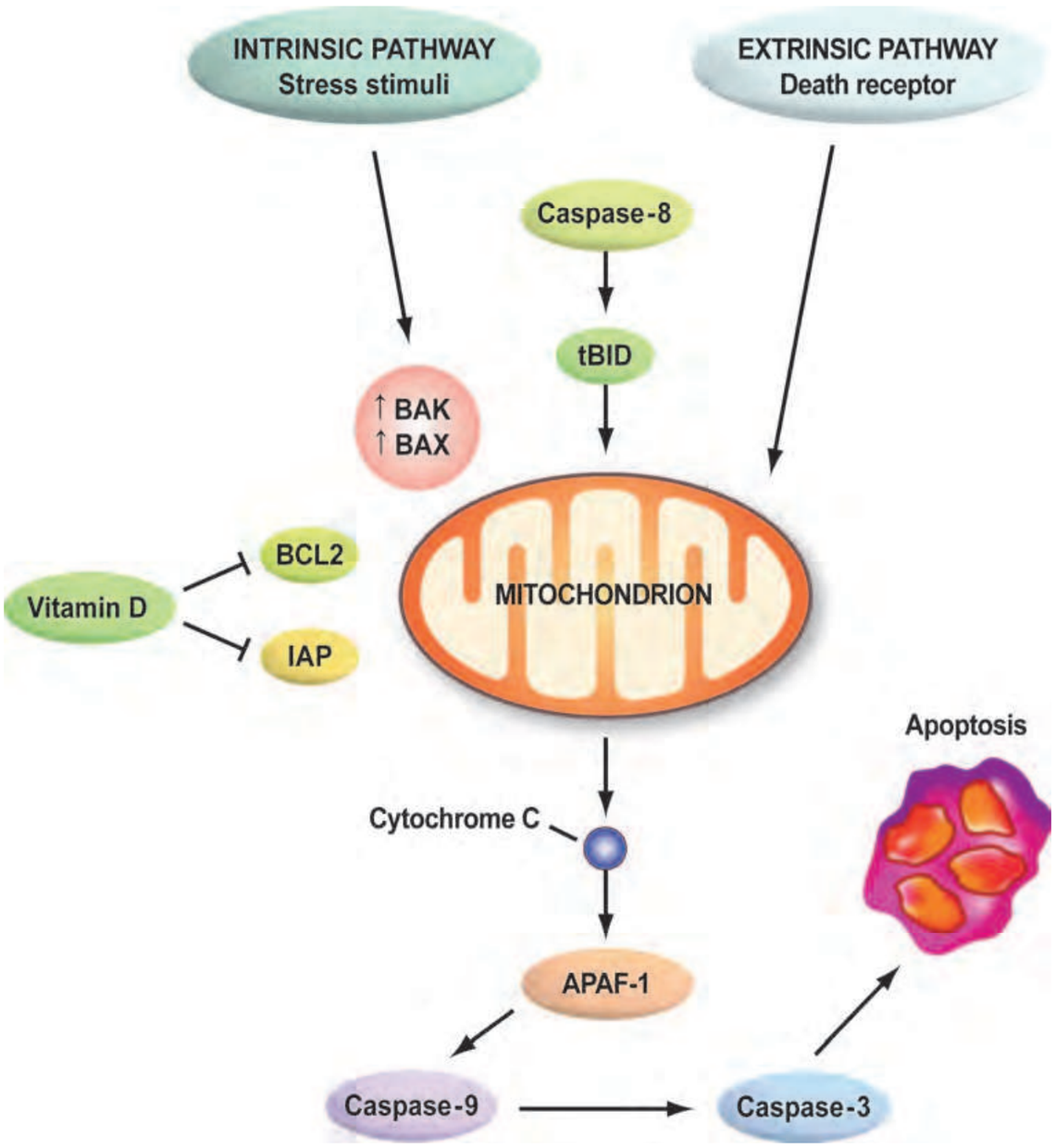

Fig. 3. Protective effect of Vitamin D through inhibition of unlimited cell growth and prevention of pro-caspase activity

4. The role of DNA repair in cancer chemoprevention

The principle of chemoprevention is based on the fact, that the treatment is able to interrupt the biological mechanisms that are involved in early carcinogenesis. It is important to know the mechanism of carcinogenesis, not only to understand the mode of action, but this knowledge gives potential for the development of novel chemopreventive agents, for future

perspectives. Chemoprevention may modify the progression of early molecular and morphological changes in the target tissues, like oncogene activation, chromosomal aberrations, mismatch-repair, and dysplasia, down regulation of DNA-repair enzymes, hyperplasia, angiogenesis, telomerase activity or anti-apoptotic effect of carcinogens. Cancer development is a long-term, multi-step process which consists of several genetic and epigenetic changes before the development of invasive cancer. The above mentioned intermediate biomarkers may serve as good tools in the indication of chemopreventive intervention.

5. Basic mechanisms of UV-induced DNA repair

The role of UV-induced DNA repair in the etiology of various malignancies has been demonstrated. Some inherited syndromes with altered DNA repair capacity increased sensitivity to mutagens manifested e.g. in abnormal sister chromatid exchange (SCE; Major et al, 1985) and have increased cancer risk (Au et al, 1996) as e.g. Down's syndrome or xeroderma pigmentosum. Wei et al (2003) studying the role of UV-induced DNA repair in the etiology of cutaneous malignant melanoma of patients with xeroderma pigmentosum (XP) suggested that reduced DNA repair capacity may contribute to susceptibility to sunlight-induced malignant melanomas among the general population as well.

UV exposure can also induce skin cancer partly by inducing immune suppression e.g. via the isomerization of *trans*-urocanic acid occurring naturally in the outermost layer of the skin, to the *cis*-isomer which can convert UV radiation into a biologically recognizable signal that activates immune suppression (Harriott-Smith & Halliday, 1988). The receptor of the *cis*-isomer is most probably the serotonin receptor itself (Walterscheid et al, 2006). Sreevidya et al (2010) demonstrated recently that platelet activating factor and serotonin receptor antagonists, known to reverse photocarcinogenesis and photoimmune suppression, can regulate DNA repair. The authors conclude that repairing DNA damage, neutralizing the activity of *cis*-urocanic acid, and reversing oxidative stress abrogates UV-induced immune suppression and cancer induction, suggesting that DNA, urocanic acid and lipid photo-oxidation serve as UV photoreceptors

UV irradiation induced DNA damage can be repaired by two major pathways: nucleotide excision repair (NER) is the pathway for removal lesions that distort DNA such as UV-induced thymine dimers, while base excision repair (BER) removes lesions resulted from exposure to exogenous or endogenous reactive oxygen species (for review, c.f. Legrand et al, 2008 and Asagoshi et al, 2010). For a detailed review of the molecular mechanisms of UV-induced DNA damage and repair c.f. Rastogi et al. (2010). NER is initiated by two distinct DNA damage sensing mechanisms: transcription coupled repair which removes damage from the active strand of transcribed genes, and global genome repair which removes damage present elsewhere in the genome (for review, c.f. Lans et al, 2010). For an efficient NER, modification of histones by acetylation and remodeling of nucleosomes is necessary (Guo et al, 2011). Genetic polymorphism may also affect the NER or BER repair capacity as it was demonstrated in case of repair enzymes XRCC1, XPA and XPD (Chang et al, 2010). The earlier dogma strictly separating the repair mechanisms of double and single strand DNA breaks seems to be outdated, since recent studies have presented increased evidence that various DNA repair mechanisms are well interlinked, as e.g. NER and mismatch repair can be involved in double strand DNA repair (for review, c.f. Ye Zhang et al, 2009).

6. Analysis of biomarkers in blood samples

Biomarkers for DNA damages and risk assessment
Considering the basic mechanism of cancer development, the most acceptable predictors of cancer risks are the DNA-damage biomarkers (see Table 3.). These damages can be provoked by exogenous or endogenous agents when DNA repair or mis-repair is in dysfunction. The unrepaired DNA damage can reduce the basic cell functions eg. maintenance of genetic integrity, triggering of cell cycle arrest, apoptosis, uncontrolled growth and other functionalities. Ultimately, damaged repair capacity leads to an increase in somatic mutations and cancer.

Methods	Target cells
Unscheduled DNA synthesis (UDS)	Lymphocytes, hepatocytes
DNA strand breaks (SGE or Comet assay)	Any living cells, germ cells
Chromosomal aberrations	Tumor cells, lymphocytes, germ cells
Micronucleus assay	Lymphocytes, bone marrow cells
Aneuploidy	Tumor cells, lymphocytes, germ cells
Telomere shortening	Any living cells
DNA-adducts and oxidation, methylation	Lymphocytes, germ cells
Nuclear p53	Any living cells
Point mutation (HPRT)	Any living cells
Mitochondrial DNA mutation	Any living cells

Table 1. Biomarkers of DNA damage

7. The use of UV-induced DNA repair for risk assessment

For assessing DNA repair capacity in human subjects exposed to various genotoxic agents in order to assess the health risk, probably the most frequently used method is the determination of UV-induced DNA repair which measures the unscheduled DNA synthesis (UDS) in cells with inhibited total repair (Bianchi et al, 1982). DNA repair measurement in liver cell lines, is also recommended by the European Union for the risk assessment of harmful chemicals, as it appears in the Regulation 440/2008/EC Part B (B.39.) and its amendments. The Regulation also allows the use of cells other than hepatocytes. The detection of a UDS response depends on the number of DNA bases excised and replaced at the site of the damage. The Regulation recommends the UDS test for the detection of substance-induced "longpatch repair" (20-30 bases), while, in contrast, the test can also detect "shortpatch repair" (1-3 bases) although with much lower sensitivity. The Regulation warns the users, that mutagenic events may be a result of non-repair, misrepair or misreplication of DNA lesions. The extent of the UDS response gives no indication about the fidelity of the repair process. In addition, it is possible that a mutagen reacts with DNA but the DNA damage is not repaired via an excision repair process. The lack of specific information on mutagenic activity provided by the UDS test is compensated for by the potential sensitivity of this endpoint because it is measured in the whole genome (Reg. 440/2008/EC).

Eldridge et al (1992) suggested a role of unscheduled DNA synthesis (UDS) in the development of human breast cancer. Kopanja et al (2009) demonstrated that cells with a deletion of the Cul4A gene which encodes a core component of cullin-based E3 ubiquitin ligase complex being over-expressed in breast cancers and correlating with poor prognosis, exhibit aberrant cell cycle regulation and reduced levels of UDS. On the other hand, nucleotide excision repair, a major mechanism involved in UV-induced DNA repair pathways can contribute to the development of resistance against drugs like cisplatin in cancer cells (Orelli et al, 2009). UV-induced UDS can reflect only a part of the total repair capacity of human cells. An easy method for the measurement of the total repair capacity can be the single cell gel electrophoresis (Comet assay) (Collins et al. 1997). A cytogenetic phenomenon, the sister chromatid exchange (SCE) can also be considered as a representative of post-replication repair (Okada et al, 2005). In the multiple end-point genotoxicology monitoring system using peripheral blood lymphocytes for the assessment of genotoxic (and leukocytes for the immune toxic) effects of environmental exposure to harmful chemicals, the repair capacity of the cells is measured by UDS, SCE and recently the Comet assay. Studies of cigarette smokers, groups of workers exposed to various chemicals e.g. uranium, butadiene (Au et al, 1996), benzene, and cytostatic drugs (Tompa et al, 1994, 2005, 2006), suggest that exposed populations can have a mutagen-induced abnormal DNA repair response. Repair mechanisms involved in the development of malignancies suggest an important role of DNA repair studies in cancer risk assessment. In an early study, Eldridge et al. (1992) demonstrated by an assay using UDS induced by chemicals and UV irradiation in early passage cultures of normal mammary epithelial cells derived from 5 different women, that UDS may be used in addressing the role of environmental agents in the development of human breast cancer.

Studies of DNA repair in populations exposed to mutagenic chemicals need to integrate chromosome aberration and other relevant assays for a more precise prediction of health risk (Au et al, 1996). When applying the so called multiple end-point genotoxicological monitoring system in Hungary, beside the use of UV-induced unscheduled DNA synthesis (UDS), we also included other biomarkers such as structural and numeric chromosome aberrations (CA), sister-chromatid exchange (SCE), mutations in the HPRT loci, early centromere separation (CS), and apoptotic capacity (AC) (Tompa, Sápi, 1989, Jakab et al, 2010, Major et al, 1999). In the present multiple end-point genotoxicology monitoring system run in Hungary (Tompa et al, 2006, c.f., Fig. 4.). DNA repair is investigated at three levels: Comet assay, UV-induced unscheduled DNA synthesis (UDS), and sister-chromatid exchange (SCE), representing the total repair capacity, the nucleotide excision repair, and the post-replication repair, respectively. Here we present data of UDS (and SCE) obtained in groups of subjects exposed to cytostatic drugs, anesthetic gases, formaldehyde, heavy and precious metals, benzene and polycyclic aromatic hydrocarbons compared to industrial controls.

8. Methods

8.1 The measurement of UV induced unscheduled DNA synthesis (UDS) in PBLs

The measurement of UDS was done according to Bianchi et al.(1982), as previously described (Tompa et al., 2005). Briefly, the separation of peripheral blood lymphocytes (PBLs) of citrated blood samples was performed by Ficoll-Hypaque density centrifugation. PBLs were irradiated in open petri dishes by UV light (24 J/m^2) and then incubated for 3 h

Methods for the multiple endpoint geno- and immune toxicology monitoring using peripheral blood lymphocytes and leukocytes in Hungary

- Information, investigation only with written consent,
- Anamnesis,
- Physical and clinical laboratory check-up,
  - Blood sampling (by venipunction), Lymphocyte separation
- Processing (standard methods)
  - Genetic toxicology (genotype):
    - Primary DNA lesions and total DNA repair (Comet assay)
    - Gene mutations in HPRT loci
    - Structural and numeric chromosome aberrations (CA)
    - Sister-chromatid exchanges (SCE)
    - UV-induced DNA repair capacity (UDS),
    - Apoptotic capacity
  - Immune toxicology (phenotype):
    - Response to lectine stimulation,
    - Phenotypic characterisation of lymphocyte subpopulations
    - Leukocyte functional tests
- Risk assessment and risk communication

Fig. 4. Biomarkers used for the multiple geno- and immuno toxicological monitoring in Hungary.

with 10 μCi/ml ^{3}H-TdR (activity: 37 MBq/ml, Amersham) in the absence or presence of 2.5 mM hydroxyurea. The degree of 'de novo' UDS was measured by scintillometry based on ^{3}H-TdR incorporation in separated lymphocytes. UDS was calculated as the difference between radioactivities of the incorporated ^{3}H-TdR in UV irradiated and control cultures (relative units).

8.2 Determination of CA and SCE frequencies

Whole blood samples were processed for studies of CA and SCE. The cell culture methods were identical in both protocols: samples of 0.8 ml heparinized blood were cultured in duplicate at 37°C, in 5% CO_2 atmosphere, in 10 ml RPMI-1640 (Sigma-Aldrich) supplemented with 20% fetal calf serum serum (Gibco Invitrogen Corporation) and 0.5 % Phytohemagglutinin-P (PHA, Gibco Invitrogen Corporation), without antibiotics. For CA and SCE analyses, the cultures were incubated for 50 hr and 72 hr, respectively. 5-Bromo-2′-deoxyuridine (BrdU, Sigma-Aldrich) used in SCE analysis to identify the first and subsequent metaphases, was added at a concentration of 5 μg/ ml at 22 hr of culture. Culture harvest, slide preparation and staining were made following standard methods using 5% Giemsa stain (Fluka) for CA (Moorhead et al., 1960), and according to the Fluorescent-Plus-Giemsa method of Perry and Wolff (1974) for SCE. All microscopic analyses were blindly performed by permanent staff. CA characterization was carried out in 100 metaphases with 46±1 chromosomes per subject according to Carrano and Natarajan (1988). Mitoses containing only achromatic lesions (gaps) and/or aneuploidy (mitoses with 45 or 47 chromosomes) were not considered aberrant. The frequencies of total premature

(early) centromere divisions (PCD i.e. the separation of centromeres during prophase/metaphase of the mitotic cycle) were scored according to Méhes & Bajnóczky (1981). Mitoses with more than three chromosomes with PCD were considered as PCD/CSG (centromere separation general).

9. Flow cytometric analysis of apoptosis and cell proliferation in PBLs

For the measurement of the percentage of apoptosis and S-phase, PBLs were separated from the blood samples on Histopaque 1077 gradients (Sigma-Aldrich) and cultured in RPMI-1640 medium (Sigma-Aldrich) supplemented with 20% fetal calf serum (Gibco Invitrogen Corporation) and 0.5 % PHA (Gibco Invitrogen Corporation) for 50 hours without antibiotics in a standard thermostat at 37°C in humidified atmosphere containing 5% CO_2. One hour prior to the termination of the cultures, 5 μg/ml BrdU (Sigma-Aldrich) was added to the cultures. Cells were washed twice with PBS, and fixed in 1 ml of ice-cold 70% ethanol and stored at –20 °C until further processing.

DNA denaturation prior to propidium iodide (PI, Sigma-Aldrich) and fluorescein isothiocyanate (FITC)-labeled monoclonal anti-BrdU (Becton-Dickinson) staining was performed at room temperature with 2M HCl containing 0.2 mg/ml pepsin (Sigma-Aldrich), according to the method of Piet van Erp et al. (1988). DNA was stained with PI and the incorporated BrdU was detected by flow cytometry with FITC-labeled monoclonal antibody.

Flow cytometric analysis was performed on a FACS Calibur (Beckton-Dickinson) flow cytometer. Data for at least 10000 lymphocytes per sample were acquired; CellQuestPro Software was used for analysis. Statistical analysis was made using the GraphPad Prism 3.02 software (GraphPad Software, Inc.), differences between the studied groups and the control were tested using the Student's t-test, $p < 0.05$ was considered as statistically significant.

10. Sample selection

Here we present the mean values (± SE) of the results of the genotoxicological investigations in 55 donors from 3 production units in the oil industry. Together with the results of the genotoxicological investigations completed with measurements of apoptosis and cell proliferation in altogether 275 subjects from oncology health care units, workers from the pharmaceutical industry, pathology and anesthesiology units, goldsmiths and galvanizers from the metal industy producing coins and mints. All subjects took part in the study voluntarily with prior informed consent, and were interviewed by a physician to collect data on age, medication, life-style (smoking and drinking habits), as well as medical and work histories in relation to known, or suspected chemical mutagens and/or to exposure to ionizing radiation.

Blood was collected by venipuncture from each of the investigated subjects: 18 ml blood in 2 VACUETTE® Coagulation tubes filled with 1 ml of 0.109 mol/l (3.2%) buffered tri-sodium citrate (Ref. No. 455322, Greiner Bio-One) for the measurements of UV induced unscheduled DNA synthesis (UDS), and 9 ml blood in 1 VACUETTE® Heparin tube coated with the anticoagulant sodium-heparin (Ref. 455051, Greiner Bio-One) for the determination of CA and SCE frequencies, and for the flow cytometric analysis of apoptosis and cell proliferation. The samples were processed immediately after blood collection. Only active smokers were considered to be "smokers". None of the individuals were addicted to alcohol, subjects

considered as "drinkers" consumed less than the equivalent of 80 g pure alcohol daily. All subjects took part in a routine clinical checkup, including hematology, liver and kidney function tests. The results were compared with control subjects without any known occupational exposure to genotoxic agents.

11. Demographic and exposure data

11.1 Exposure to aromatic hydrocarbons

Among oil industry workers, in the first group we have investigated 27 workers exposed mainly to benzene from a plant producing aromatic compounds, such as benzene (26 men and 1 woman, 186 investigations). The second and third groups comprised of 14 bitumen producers (13 men and 1 woman, 107 investigations) and 14 coke producing workers mainly exposed to PAH's (only men, 87 investigations), respectively. Mean ages were 34.7± 1.6 years (range 24-55) for the benzene producers, 40.4± 2.4 years (range 26-55) for the bitumen exposed workers, and 32.1± 1.4 years (range 25-42) for the coke producers, respectively. Mean percentages of current smokers were 22.2 % among benzene producers, 50.0 % among bitumen exposed workers, and 28.6% among the coke producers, respectively. Mean frequencies of "drinkers" were 81.5% in the benzene exposed group, 78.6% among bitumen producers and 71.4 among coke producers, respectively.

11.2 Exposure to cytostatic drugs

Altogether 138 subjects of hospital staff from health care units exposed to various cytostatics during the treatment of cancer patients, were divided into two groups. The first group of health care workers working without adequate protection consisted of 23 subjects (1 man and 22 women, 45 investigations), while the other group of the health care workers using protective devices during work consisted of 115 subjects (8 men, 107 women, 131 investigations), respectively. In the group of the pharmeceutical industry workers producing cytostatics there were 36 subjects (4 men, 32 women, 97 investigations). Mean ages were 38.9± 2.1 years (range 24-57) for the health care personnel without and 33.7± 0.93 years (range 20-62) with protection, respectively. Mean age among pharmeceutical industry workers exposed to cytostatics was in the range of 20-55 years (mean 36.0±1.6 years). Mean percentages of active smokers were 47.8 % among health care personnel without protection, 54.8 % among health care personnel with protection, and 44.4% among pharmaceutical industry workers, respectively. Mean frequencies of "drinkers" in the above listed groups were 13.0 % among health care personnel without protection, 52.2 % among health care personnel with protection, 44.4% among pharmaceutical industry workers, respectively.

11.3 Exposure to anesthetic gases and formaldehyde

Hospital staff from anesthesiology units were also divided into two groups: the first consisted of 30 subjects exposed to the anesthetic gas halothane (4 men and 26 women, 34 investigations), while in the other 28 workers were exposed to anesthethic gases isoflurane and sevoflurane (2 men and 26 women, 28 investigations). Pathology staff consisted of 21 subjects (only women, 21 investigations) exposed to formaldehyde. Mean ages of anesthesiology unit workers exposed to halothane and anesthetic gases other than halothane were 39.0±1.8 and 40.4±1.36 years (ranges 23-57 and 29-55), respectively. Mean age in the groups of pathology staff was 43.3±2.0 years (range 26-60). The frequencies of active smokers were 16.7% among anesthesiologists exposed to halothane, 35.7% among

anesthesiologists exposed to anesthetic gases other than halothane and 23.8 % in pathology workers, respectively. The frequencies of 'drinkers' were 46.7% among anesthesiologists exposed to halothane, 64.3% among anesthesiologists exposed to anesthetic gases other than halothane and 57.1 % in pathology workers, respectively.

11.4 Exposure to heavy metals

In the group of the 22 goldsmiths' and galvanizers there were 14 men and 8 women (22 investigations). The mean age in the group of goldsmiths and galvanizers was 51.5±1.6 years (range 34-60). There were 31.8% smokers and 45.5% 'drinkers' in this group.

12. Control subjects

The results of the investigated subjects in oil industry groups were compared with 87 industrial controls (53 men and 34 women), selected from the administrative staff in the oil industry, without known previous occupational exposure to genotoxic agents. Mean age was 38.6±1.1 years (range 20-67) for this group of the industrial controls. There were 42.5% current smokers and 50.6% 'drinkers' among industrial controls.

In case of the investigated health care, pharmaceutical and metall industry subjects the results were compared with 57 industrial controls without known previous occupational exposure to genotoxic agents (11 men and 46 women). The controls were selected from health care personnel and from the administrative staff in the metal industry producing coins and mints, without known previous occupational exposure to cytostatics and other genotoxic agents. The mean age was 44.1±1.7 years (range 22-69). The percentages of active smokers and 'drinkers' were 24.6% and 45.6% among industrial controls, respectively.

13. Results

The results of the UDS measurements and the mean frequencies of SCE and CA in the workers in the oil industry are summarized in Table 2A. UDS was significantly decreased among benzene (p=0.00067) and bitumen (p=0.00788) exposed donors. Similarly, a significantly decreased UDS (p=7.04E-8) was also observed among coke producers. CA was significantly increased in each group of the exposed donors. Similarly to CA, an increase in the mean values of SCE could be observed in each group of the exposed, although the increases were only significant among the benzene and bitumen exposed (p=0.000602 and p=0.001204, respectively).

Table 2B summarizes the cytogenetic parameters in cultured PBLs among the oil industry workers. Mean frequencies of cells with aberrations (aberrant cells, AB.C) were increased in all groups of the oil industy workers. The aberrations in all groups were mainly of the chromatide type breaks. Similarly to the CA and AB.C values, mean PCD(CSG) values were also significantly increased in all groups of oil industry workers (p=1.238E-21, p=9.7E-15 and p=1.61E-13, respectively).

The results of flow cytometric and UDS measurements, and the mean frequencies of SCE and CA are summerized in Table 3A. Mean apoptosis values were significantly increased in two groups of the cytostatics exposed subjects (health care personnel without protection, p= 0.0047 and pharmaceutical industry workers, p=0.0056), in anesthesiologists exposed to halothane (p=0.02451) and in formaldehyde exposed subjects (p=0.00066). Apoptosis was also increased among anesthesiologists exposed to anesthetic gases other than halothane,

but this increase was only at the 10% level (p=0.09427). In contrast, apoptosis was significantly reduced among goldsmiths and galvanizers (p=0.02203). Cell proliferation (the percentage of S-phase) was significantly decreased in both groups of health care personnel exposed to cytostatics (p=0.00079 and p=3.65E-8, respectively) and in both groups of anesthesiologists (p= 7.42E-8 and p=0.003324, respectively). In the group of the pharmeceutical industry workers, S-phase showed a significant increase (p=3.21E-10). A statistically significant decrease in UDS was observed in the groups of health care personnel exposed to cytostatics without protection (p=0.057927) and the workers from the pharmaceutical industry (p=0,04959). SCE was only significantly increased in the group of the health care personnel without adequate protection (p=0.000416). CA was significantly increased in the groups of the pharmaceutical industry workers (p=0.01515) and the pathologists exposed to formaldehyde (p=0,053). Among anesthesiologist exposed to halothane, CA was also increased, but the significance was only at the 10% level (p=0.08429).

Groups	Exposure	No of investigations	UDS rel.unit		SCE 1/mitoses		CA %	
			mean	±SE	mean	±SE	mean	±SE
Industrial controls	-	87	7.11	0.37	5.71	0.12	1.60	0.24
Benzene producers	Benzene	186	5.63*	0.21	6.20*	0.08	2.47*	0.17
Bitumen producers	Bitumen	107	6.00*	0.33	6.43*	0.10	2.98*	0.26
Coke producers	PAHs	87	4.42*	0.30	5.90	0.11	2.49*	0.22

* Significant to the industrial controls (Student's t-test. p<0.05)

Table 2. a. Mean values (± SE) of UV induced unscheduled DNA synthesis (UDS, relative units), the frequencies of sister chromatid exchanges (SCE, 1/mitoses) and chromosome aberrations (CA, %) in cultured peripheral lymphocytes among oil industry workers

Groups	Exposure	Number of investigations	AB.C %		CHT %		CHS %		PCD(CSG) %	
			mean	±SE	mean	±SE	mean	±SE	mean	±SE
Industrial controls	-	87	1.58	0.25	1.14	0.20	0.42	0.11	0.95	0.25
Benzene producers	Benzene	186	2.41*	0.16	1.63*	0.14	0.84*	0.09	6.18*	0.40
Bitumen producers	Bitumen	107	2.75*	0.24	1.64*	0.16	1.34*	0.18	5.33*	0.43
Coke producers	PAHs	87	2.40*	0.22	1.87*	0.20	0.67	0.11	6.05*	0.56

*Significant to the controls (Student's t-test. p<0.05)

Table 2. b. Mean values (± SE) of the frequencies of cells with chromosomal aberrations (AB.C, %), chromosomal aberrations of the chromatide (CHT, %) and chromosome type (CHS, %) and the frequencies of premature centromere divisions with centromere separation general (PCD/CSG, %) in cultured peripheral lymphocytes among oil industry workers

Groups	Exposure	Number of investi-gations	Apoptosis %		S-phase %		UDS rel.unit		SCE 1/mitoses		CA %	
			mean	±SE	mean	±SE	mean	±SE	mean	±SE	mean	±SE
Controls	-	57	5.85	0.27	20.93	1.20	5.99	0.35	6.09	0.11	1.81	0.24
Health care personnel without protection	Cytostatics	45	8.39*	0.83	15.07*	1.29	4.92*	0.44	6.94*	0.20	2.47	0.43
Health care personnel with protection	Cytostatics	131	5.90	0.33	12.79*	0.57	5.83	0.25	6.36	0.07	1.61	0.22
Pharmaceutical industry	Cytostatics	97	8.78*	0.94	41.81*	2.19	4.72*	0.30	6.16	0.14	2.62*	0.22
Anesthesiologists	Halothane	34	7.87*	0.81	11.16*	1.11	5.92	0.41	6.25	0.13	2.62**	0.39
Anesthesiologists	Other than halothane	28	8.31	1.42	15.41*	1.35	5.57	0.49	6.36	0.15	1.30	0.27
Pathology staff	Formalde-hyde	21	10.46*	1.17	25.24	2.38	4.63	0.86	6.36	0.26	3.05*	0.62
Goldsmiths and galvanizers	Heavy and precious metals	22	4.84*	0.36	22.84	2.14	5.21	0.55	6.14	0.13	1.77	0.38

* Significant to the controls (Student's t-test. $p<0.05$)
**Significant to the controls (Student's t-test. $p<0.1$)

Table 3. a. Mean values (± SE) of apoptosis induction (%), cell proliferation (S-phase), UV induced unscheduled DNA synthesis (UDS, relative units), the frequencies of sister chromatid exchanges (SCE, 1/mitoses) and chromosome aberrations (CA, %) in cultured peripheral lymphocytes. The investigated groups were: health care personnel and workers in the pharmaceutical industry exposed to cytostatics, anesthesiologists, pathology unit personnel exposed to formaldehyde and goldsmiths and galvanizers in the metal industry exposed to heavy and precious metals

Table 3B represents the cytogenetic data of donors exposed to cytostatics, anesthetic gases, formaldehyde and metals. Aberrations were mainly of the chromatid type, with the exception of health care personnel without protection, where a nearly equal frequency of chromatid and chromosome type aberrations were scored. PCD/CSG was significantly increased in parallel to the increases of CAs and AB.C., among workers from the pharmaceutical industry ($p=0.00356$) and pathologists exposed to formaldehyde ($p=0.004608$). However, mean percentages of PCD/CSG were (not significantly) increased among cytostatics exposed health care personnel with protection and anesthesiologists exposed to anesthetic gases other than halothane, although the mean values of CAs and AB.C were not increased in these groups. On the contrary, in case of the anesthesiologists exposed to halothane, PCD/CSG was not increased, but CAs and AB.C were.

14. Discussion

14.1 Gene and environmental interactions

In the present study, the level of environmental genotoxic stress was characterized by the frequencies of chromosomal aberrations (CA). Au et al. (1996) suggested that the

Groups	Exposure	Number of investigations	AB.C %		CHT %		CHS %		PCD(CSG) %	
			mean	±SE	mean	±SE	mean	±SE	mean	±SE
Controls	-	57	1.63	0.22	1.25	0.22	0.56	0.14	4.71	0.55
Health care personnel without protection	Cytostatics	45	2.20	0.33	1.20	0.30	1.27*	0.23	3.67	0.50
Health care personnel with protection	Cytostatics	131	1.47	0.19	0.83	0.14	0.78	0.14	5.71	0.48
Pharmaceutical industry	Cytostatics	20	2.55*	0.21	1.90*	0.18	0.71	0.12	7.07*	0.39
Anesthesiologists	Halothane	34	2.38**	0.33	1.53	0.29	1.09*	0.26	3.41	0.75
Anesthesiologists	Other than halothane	30	1.19	0.27	0.74	0.21	0.44	0.15	6.43	1.61
Pathology staff	Formaldehyde	21	2.80*	0.61	2.35*	0.46	0.70	0.26	8.80*	1.07
Goldsmiths and galvanizers	Heavy and precious metals	22	1.50	0.33	1.18	0.35	0.59	0.23	3.95	0.75

* Significant to the controls (Student's t-test. $p<0.05$)
** Significant to the controls (Student's t-test. $p<0.1$)

Table 3. b. Mean values (± SE) of the frequencies of cells with chromosomal aberrations (AB.C, %), chromosomal aberrations of the chromatide (CHT, %) and chromosome type (CHS, %) and the frequencies of premature centromere divisions with centromere separation general (PCD/CSG, %) in cultured peripheral lymphocytes. The investigated groups were: health care personnel and workers in the pharmaceutical industry exposed to cytostatics, anesthesiologists, pathology unit personnel exposed to formaldehyde and goldsmiths'and galvanizers in the metal industry exposed to heavy and precious metals

measurement of CA yields should be integrated in the assessment of health risk when DNA repair responses are studied. In the Hungarian multiple end-point genotoxicology monitoring system introduced in the late 1980s, the two key biomarkers have been the frequencies of gene mutations in the hprt loci (Tompa, A., Sápi, E., 1989) and CAs (Tompa, A., et al, 1994). In the present study, CA yields were increased in exposures to cytostatic drugs, halothane, formaldehyde, benzene and PAHs, as compared to controls, indicating a genotoxic stress in these populations (see *Tables 2A and 3A*). Chromatid type aberrations (CHT) representing rather the damages of DNA bases and single strand breaks, and chromosome type aberrations (CHS) representing double stranded DNA breaks that formed in cells mostly prior to entering the cell cycle, were increased in groups exposed to cytostatic drugs, formaldehyde, heavy and precious metals, benzene, and PAHs *(see Tables 2B and 3B)*. An Italian team led by Bonassi in 2000 and the Nordic Study Group correlated the occurrence of chromosomal aberrations in human PBL cells with cancer risk in human populations. These prospective cohort studies have shown a significant (2.3-2.6 fold) increase in cancer in those individuals, who had permanent high level of chromosomal

aberrations. This seems to verify the hypothesis; that an increase of chromosomal aberration in itself may increase cancer risk. Therefore the intervention should take place in advance, when these alterations have just appeared in the peripheral blood lymphocytes (PBL). Genetic polymorphisms, eg. mutations of detoxification enzymes glutathione S-transferase (GST, GSTP1, and GSTM1) seem to be a risk factor for lung, head and neck cancer. Sequence variation in a DNA-repair gene, i.e. XPD have been associated with high lung cancer incidence. Chromosomal aberrations and loss of heterozygosity (LOH), especially 3p and 9p losses are important in all types of lung cancer too. Nuclear p53 mutation is a predictor of cancer, because the mutant cells are not able to respond properly to apoptotic signals and daughter cells inherit the mutation and genetic instability with the message of cancer development (Gretarsdottir 1998).

14.2 DNA repair capacity in the exposure groups

UV-induced DNA repair capacities (UDS) in PBLs were decreased, while CA yields (including the chromosome type aberrations) were increased in each groups exposed to aromatic hydrocarbons (benzene and PAHs) when compared to the controls in accordance with our earlier observations (Tompa et al 2005). Exposure to benzene, which was present in the ambient air could produce DNA strand breaks and oxidation of the bases in correlation with the level of its metabolite phenylmercapturic acid in urine (Sorensen et al 2003). It means that the higher is benzene in the ambient air, the higher can be the level of benzene-induced DNA damage. It can trigger the repair mechanisms such as BER, NER and double strand break DNA repairs involved in the removal of benzene-induced DNA lesions (Hartwig, 2010). Ambient air PAH levels and their diol epoxide metabolites also correlate with DNA base oxidation and strand breaks in the exposed human populations (Ruchirawat et al 2010; Zhong et al 2010). However, several studies demonstrated reduction in DNA repair capacity (measured by different methods) among benzene or PAHs exposed workers (Tompa et al 2005; Keretetse et al 2008; Chanvaivit et al 2007; Ruchirawat et al 2010). Using the Comet assay for the characterization both of the level of primary DNA lesions and repair in PBLs of petrol attendants with occupational exposures longer than 1 year, Keretetse et al (2008) demonstrated that the genotoxic volatile organic compounds such as benzene and certain PAHs can inhibit the repair of single-strand breaks. The reduction of the excision repair capacity is influenced by the polymorphism of the involved repair genes (Shi et al 2004; Pavanello et al 2005).

DNA repair capacities of PBLs were also reduced while CA yields were increased among the hospital nurses and pharmaceutical industry workers occupationally exposed to various anticancer drugs producing DNA strand breaks or base alterations, compared to the controls and to the subjects with proper protection. The same was observed in the case of pathology unit staff members exposed to formaldehyde. Exposure to halothane, although increased the CA frequencies among the exposed anesthesiologists as compared to the controls, did not affect the UDS levels. Among workers exposed to heavy or precious metals with potency to induce oxidative damages of DNA, no alterations were observed in the investigated biomarkers when compared to the controls. In an early study, Celotti et al (1990) demonstrated increased UV-induced UDS in the PBLs of patients treated with antineoplastic drugs, while no alteration compared to the controls were observed among the nurses handling and administering the drugs. Studies demonstrated that careless handling of antineoplastic drugs can lead to exposure of personnel (Sorsa & Anderson 1996; Tompa et

al 2006). Again reduced UDS capacity was observed among hospital nurses occupationally exposed to ethylene oxide and ^{222}Rn from the local tap-water (Tompa et al 1999; Major et al 1996). In contrary, UDS was increased compared to the control among nurses using horizontal air flow cabinets for the preparation of cytostatic infusions (Jakab et al 1999). Polymorphism of the repair genes XRCC1 and XRCC3 can contribute to increase the genetic damage in susceptible subjects with chronic exposure to cytostatic drugs (Laffon et al 2005; Cornetta et al 2008). Formaldehyde, an endogenous cellular aldehyde often used in pathology and anatomy laboratories is a well-known human mutagenic carcinogen although evidence of genotoxic effects in human PBLs is insufficient (Costa et al 2008; Jakab et al 2010). In our study a significant increase of CA yields and apoptotic capacity was observed among the exposed donors (Jakab et al 2010). Formaldehyde is a capacious inducer of DNA-protein crosslinks beside base modifications. Speit et al (2000) investigating the base excision and crosslink repairs suggested that a disturbed excision repair can have more severe consequences with regards of CA formation after formaldehyde exposure than a disturbed crosslink repair. Costa et al (2008) found no significant effect of genetic polymorphism of DNA repair enzymes on the investigated genotoxic end points (micronuclei, SCE, and primary DNA lesions determined by the comet assay).

15. DNA-repair and apoptosis

UDS was reduced; however apoptotic capacity was increased in some groups exposed to genotoxic chemicals such as anticancer drugs, benzene and polycyclic aromatic hydrocarbons (PAHs) but not UV (see *Tables 2A and 3A*) during the monitoring indicating an exposure-related decrease in UV-induced excision DNA repair capacity among these donors, and suggesting a relationship between UV-induced repair and apoptotic capacities of peripheral blood lymphocytes. However, sister-chromatid exchanges (SCE), probably reflecting post-replication repair events mediated by homologous recombination (Okada et al, 2005), therefore considered as biomarkers of total DNA repair, were increased among hospital nurses exposed to cytostatics, and workers exposed to benzene and PAHs, compared to the controls.

Apoptosis is energy dependent and programmed cell death is regulated by several biochemical mechanisms [Evan & Vousden 2001]. Three main pathways are known of apoptotic events. One is stimulated by the death receptors and caspase 8 activation, the second is an intrinsic pathway with activation of mitochondrial changes trough caspase 9 and 3 activation. The third mechanism occurs through cytotoxic T cells with the help of perforin production, and granzyme A and B stimulation with caspase 10 activation. Each pathway activates its initiator caspase. Only granzyme A works independently of caspases. According to our present knowledge, approximately 14 caspases have been identified as initiators of apoptosis and proteolytic enzymes. Inhibition of apoptotic processes can be a significant cause of cancer development or autoimmune diseases. Excessive apoptosis is present in neurodegenerative diseases or in HIV infection. In contrast, tumor cells can resist apoptotic signals leading to an unlimited growth of malignant cells, production of anti-apoptotic proteins like Bcl-2, mutated P53, or down regulation of pro apoptotic Bax protein. P53 mutation is very common in human cancers; more than 50% of malignant tumors express mutant P53 cells. During cell replication the DNA repair is able to recognize DNA damages and keep the cell in G1/S phase. If the damage is irreparable, the apoptotic signal

is activated, although damaged or mutated P53 does not respond properly to this physiological signal (see Fig. 5.)

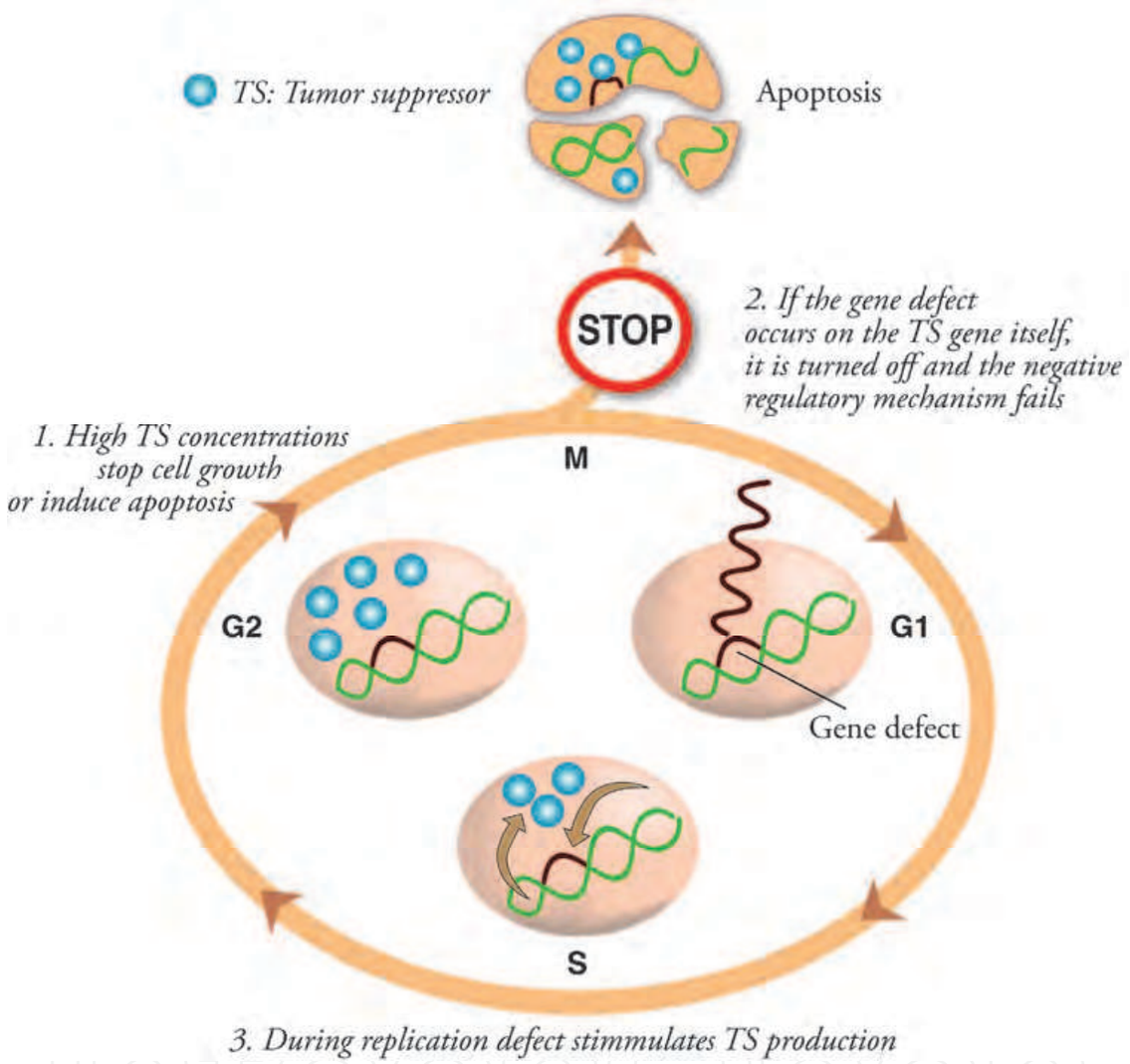

Fig. 5. The cell cycle and apoptosis

The gene p53 can play a key role in response to DNA damage by activating a G1 cell cycle arrest (Geyer et al, 2000). Squires et al. (2004) studying the DNA structure of replication forks in normal human and NER-deficient XP cells observed that replication associated DNA double strand breaks do not accumulate in p53 proficient human cells and proposed the prevention of DSB accumulation at long lived single stranded DNA regions in stalled-replication forks as a major mechanism of maintenance of genome stability by p53. Geyer et al (2000) reported a G1 to S phase delay of the mitotic cell cycle after UV treatment in GM6419 cells expressing dominant negative p53 mutations and suggested that unrepaired DNA damage was the signal for the stabilization of p53 and a subsequent G1 phase cell cycle arrest in UV-irradiated cells. A homeostatic regulator, the wild-type p53-induced phosphatase (Wip1) which is induced by p53 in response to e.g. UV-induced DNA damage is also involved in DNA repair and cell cycle

checkpoint pathways. Wip1 can be activated via both the JNK c-Jun and p38 MAPK-p53 signaling pathways, and a temporal induction of Wip1 depends largely on the balance between c-Jun and p53, which compete for JNK binding (Song et al, 2010). In wild-type but not in c-Jun (and c-Fos) null human cells a clear up-regulation of trex1 was observed after UV irradiation, and upon genotoxic stress a translocation of trex1 into the nucleus was suggested (Christmann et al, 2010) also indicating a strong relationship between UV-induced DNA damage and apoptotic capacity of human cells. Protein p21 is also a key component in p53 regulated cell cycle control and apoptosis, directing an anti apoptotic response following DNA damage as a major transcriptional target of p53 (Hill et al, 2008). Moreover, UV irradiation can also trigger p21 proteolysis, which seems to be in correlation with increased apoptosis (Soria et al, 2008). Data obtained on p53 binding on the p21 promoter suggest that the nature of DNA damage is itself the key factor for p53-regulated expression of target genes such as p21 and the subsequent cellular outcome (Hill et al, 2008).

16. Conclusions

During the multistep process of carcinogenesis several genetic and epigenetic changes accumulate in the target tissue through mutations, alkylation and formation of DNA and protein adducts. The modifications in cell cycle, proto-oncogenes, oncogenes and induction of chromosomal aberrations represent the arsenal of biomarkers showing early signs of cell transformation. Chemoprevention of carcinogenesis is based upon knowledge of the mechanisms of carcinogenesis, eg. inhibition of cell proliferation, signal transduction, increases in tumor suppression, activation of antipromotion, changes in metabolic activation and enhancement of apoptotic activity. Chemopreventive agents are usually selected according to cancer type (lung, colon, breast, oral cavity, bladder and prostate) or on the known mechanism of cancer development. The other, most effective approach to prevent cancer is to avoid carcinogenic agents (primary prevention). Biomarkers can be utilized as indicators of exposures, effects and individual susceptibility to cancer. Proper selection of biomarkers in relation to exposure may have a great impact on the reliability of mechanism of action. Recent developments in genomics provide an opportunity to investigate several oncogenes, tumor-suppressor genes, phenotypic changes in proteins simultaneously. Biomarkers such as the occurrence of high level of chromosomal aberrations can also indicate the need of intervention in high risk groups. An introduction of chemoprevention in order to avoid or delay cancer development can be advised in those cases, where removal of environmental hazards have not been efficient and the subjects have already sufferred irreversible genetic damages.

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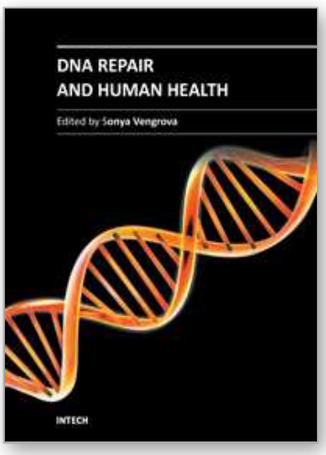

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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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