

## DNA Adducts

J. PARTHIBAN<sup>1</sup>, K. T. SHANMUGAM<sup>2</sup>, N. ARAVINDHA BABU<sup>3</sup> and KESAVAN<sup>4</sup>

<sup>1</sup>Department of Omfs, Tagore Dental College And Hospital, India.

<sup>2</sup>Department of Oral Pathology, Madha Dental College and Hospital, India.

<sup>3</sup>Department of Oral Pathology and Microbiology (COCPAR),  
Sree Balaji Dental College & Hospital, Bharath University, Chennai, India.

<sup>4</sup>Department of Oral Pathology, Madha Dental College and Hospital, India.

DOI: <http://dx.doi.org/10.13005/bpj/660>

(Received: August 15, 2015; accepted: September 20, 2015)

### INTRODUCTION

In molecular genetics, a DNA adduct is a piece of DNA covalently bonded to a (cancer-causing) chemical. This process could be the start of a cancerous cell, or carcinogenesis. DNA adducts in scientific experiments are used as biomarkers of exposure<sup>1</sup> and as such are themselves measured to reflect quantitatively, for comparison, the amount of carcinogen exposure to the subject organism, for example rats or other living animals. Under experimental conditions for study, such DNA adducts are induced by known carcinogens, of which commonly used is DMBA (7,12-dimethylbenz(a)anthracene).

The presence of such an adduct indicates prior exposure to a potential carcinogen, but does not by itself indicate the presence of cancer in the subject animal<sup>2</sup>.

#### Chemicals that form DNA adducts include

- acetaldehyde, a significant constituent of tobacco smoke
- cisplatin, which binds to DNA and causes crosslinking, leading to death of the cell
- DMBA (7,12-dimethylbenz(a)anthracene)
- malondialdehyde, a naturally occurring product of lipid peroxidation<sup>3</sup>

#### DNA adducts include(examples)

- etheno-DNA adducts:
  - N(6)-etheno-2'-deoxyadenosine (epsilon dA) and
  - N(4)-etheno-2'-deoxycytidine (epsilon dC)
- When a chemical binds to DNA, the DNA becomes damaged, and proper and complete replication cannot occur to make the normal intended cell. This could be the start of a mutation, or mutagenesis, and, without proper DNA repair (DNA repair happens naturally under normal circumstances), this can lead to carcinogenesis, the beginnings of cancer<sup>3</sup>.

Genotoxic carcinogens initiate the carcinogenic process in mammalian cells by damaging DNA. Where the damage results in attachment of the carcinogen, or its activated metabolite(s) to DNA, the resulting DNA adducts can lead to errors in replication and a permanent alteration in the genetic code. Mutations in critical genes can result in malignant transformation. Several techniques are available with sufficient sensitivity to detect DNA adducts formed as a consequence of occupational or environmental exposure to carcinogens<sup>4</sup>.

Detection and identification of DNA adducts in human DNA can provide important clues

to the aetiology of cancer. Strategies that inhibit the formation of DNA adducts may have utility in chemoprevention of cancer, and monitoring of DNA adduct formation and removal offers an intermediate biomarker for the assessment of carcinogen exposure and risk of cancer<sup>4</sup>.

#### **DNA adduct and tobacco carcinogenesis**

DNA adducts are physical complexes formed between reactive chemical species and sites within the DNA molecule and have been proposed as potential markers of 'biologically effective dose' from exposure to tobacco carcinogens that may help to provide an integrated measure of carcinogen exposure relevant to individual cancer risk assessment.<sup>5</sup>

#### **DNA adducts associated with lung cancer**

Studies of DNA adducts in lung cancer patients have indicated higher adduct levels in lung tissue of cancer cases and in their peripheral white blood cells compared with controls. Higher adduct levels were reported in lung tissue from women compared with men. Heavy smokers were reported of high adduct levels in bronchoalveolar cells which was associated with higher cancer mortality, though not specifically lung cancer. DNA adducts induced in vitro have been associated with lung cancer risk in case ± control studies.

#### **DNA adducts and cancers of the bladder, head and neck, pancreas and uterine cervix**

DNA adduct levels in white blood cells were significantly associated with bladder cancer risk and a series of studies have shown that smoking was associated with smoking related adducts in the oral cavity and larynx. Particularly striking was the specific adducts in gingival tissue derived from unsaturated aldehydes in cigarette smoke. A small study of pancreatic cancer patients reported higher levels of several DNA adduct species in non-tumorous pancreatic tissues from cases compared with control tissues. Smoking is a risk factor in cervical cancer and DNA adducts related to smoking have been observed in cervical cells of smokers.<sup>5</sup>

#### **DNA adducts and p53**

The important mechanistic hypotheses on p53 mutational spectrum and smoking raise

significant challenges for clinical and epidemiological investigators to translate these insights into human populations. Early small studies suggested that aromatic-DNA adduct levels were increased in tissues from patients with p53 mutant lung cancer compared with cases bearing non-p53 mutant tumors, while another study reported only a weak association between PAH±DNA adduct levels in lung tissue and p53 mutations. Our group found that lung cancer patients with high hydrophobic ±DNA adduct levels in non-tumorous lung tissue (above the median adduct level) were threefold more likely to have a tumor containing a p53 mutation. This association was significant, even after adjusting for smoking status. In contrast, in a study of bladder cancer, 4-aminobiphenyl ±DNA adducts were not found to be associated with the p53 mutational status of tumors. Larger studies with carefully collected smoking and lifestyle histories are necessary to define the relationship of DNA adduct burden in vivo and the p53 mutational status and spectra of human lung cancer<sup>6</sup>.

#### **Quantitation of DNA adducts:**

Quantitation of DNA adducts in human tissues has been achieved with highly sensitive techniques based on adduct radiolabeling, antisera specific for DNA adducts or modified DNA, and/or adduct structural characterization using chemical instrumentation. Combinations of these approaches now promise to elucidate specific adduct structures and provide detection limits in the range of 1 adduct/10 nucleotides. Documentation of human exposure and biologically effective dose (i.e., chemical bound to DNA) has been achieved for a wide variety of chemical carcinogens, including polycyclic aromatic hydrocarbons (PAHs), aromatic amines, heterocyclic amines, aflatoxins, nitrosamines, cancer chemotherapeutic agents, styrene, and malondialdehyde. Due to difficulties in exposure documentation, dosimetry has not been precise with most environmental and occupational exposures, even though increases in human blood cell DNA adduct levels may correlate approximately with dose. Perhaps more significant are observations that lowering exposure results in decreasing DNA adduct levels.

DNA adduct dosimetry for environmental agents has been achieved with dietary contaminants. For example, blood cell polycyclic aromatic hydrocarbon-DNA adduct levels were shown to correlate with frequency of charbroiled meat consumption in California firefighters.<sup>7</sup>

#### Importance of adduct identification

Generally, the measurement of total adducts in DNA is considered an adequate indicator of genotoxicity. Such total adduct measurements will clearly include all the modified DNA bases from the compound and from each of its metabolites. Despite the fact that only some of these adducts

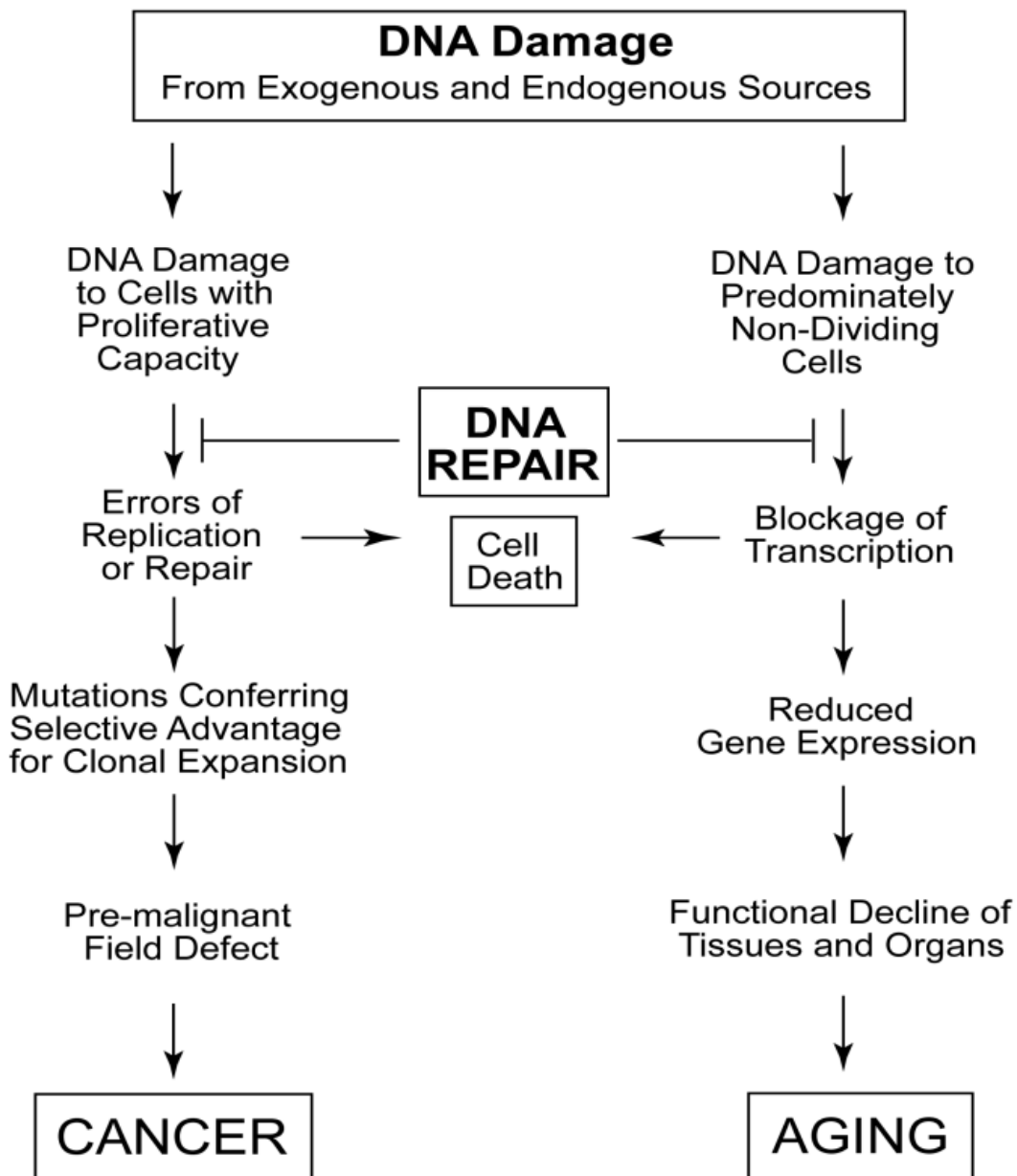


Fig. 1: Schematic representation of DNA damage & its consequences

may be of particular mutagenic significance (e.g., O6- adducts on guanine) the measurement of their sum should correlate with the amount of the significant ones, and is therefore a valid biomonitor of genotoxicity.

Recent research has shown that in addition to exposure to exogenous electrophiles, the mammalian genome is also under attack from endogenous DNA reactive substances.

Normal cellular function is known to release electrophiles. Many of these agents are highly reactive, and thus, do not need further metabolic activation. Various types of endogenous

DNA damage include those from DNA instability, errors in replication and repair, oxidatively damaged bases and adducts derived from reaction of bases with aldehydic lipid peroxidation products.

### CONCLUSION

The biological significance of a type of DNA adduct is related to several factors, including the efficiency of conversion to mutation, the amounts of similar endogenous adducts, and the variety of exogenous DNA adducts found in DNA from humans. Hence, DNA adducts are likely to play an important role in human risk for cancer induction and progression, but the quantitative aspects of this relationship remain to be determined

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