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Commentary

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Implications of DNA damage and DNA repair on human diseases

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Cellular DNA damage is implicated in the aetiology and progression of many different types of human disorders and diseases. Much of the current research in the DNA damage field is devoted towards understanding the mechanisms and biological implications of DNA lesions that turn into genetic mutations; mutations which ultimately lead to the development of cancer. DNA damage is also implicated in the development of other prevalent human diseases ranging from neurodegenerative disorders such as Alzheimer's disease to chronic obstructive pulmonary disease (COPD). The levels of DNA damage in cancer cells and in other diseased cells are elevated in comparison to the lesion levels found in normal cells. There now exists an abundance of laboratory research focused on characterising and understanding the DNA repair capacity and DNA repair mechanisms utilised by both diseased and normal cells. And because cancer is the leading cause of early mortality worldwide, there is a predominant and accelerating emphasis on clarifying the overlapping repair pathways and repair proteins utilised by cancer cells.

Cancer cells can be eradicated by the intentional induction of DNA damage, but DNA damaging agents and treatments must be selectively targeted so as not to induce damage to normal cells and tissues. Alternatively, there exists the capacity to sensitise cancer cells to DNA damage inducing agents and treatments through the direct inhibition of DNA repair proteins or alteration of the DNA damage response. The development of effective treatments targeted towards DNA repair pathways of cancerous, diseased or normal cells requires a comprehensive understanding of the structural and functional biology and repair mechanisms of the DNA repair and accessory proteins utilised in the interconnected DNA repair pathways of the different cell types. This Special Issue of *Mutagenesis* entitled *Implications of DNA Damage and DNA Repair on Human Diseases* includes submissions from acknowledged experts on measuring and characterising DNA damage in human diseases as well as submissions from recognised experts in evaluating the structural and functional biology of DNA repair proteins in the context of human cancers and emerging treatment strategies for those cancers. The issue opens with a comprehensive review by Møller *et al.* on the levels of DNA damage found in high prevalence diseases in high income countries (1). The authors utilised literature sources to critically evaluate and compare/contrast the levels of DNA strand breaks (SBs) as measured by the comet assay in the 10 most prevalent human diseases. The detected SBs in leukocytes for certain diseases, such as coronary artery disease, diabetes, Alzheimer's and COPD, showed 2× higher levels of SBs vs healthy controls. There are limited numbers of case–control studies focusing on cancers that reported SB measurements using the comet assay, so it was challenging for the authors to determine if SBs were higher in neoplastic vs non-neoplastic diseases. In the next report, Tretyakova and coworkers demonstrate via mass spectrometry-based measurements that carcinogen–DNA adduct measurements can be utilised to evaluate lung cancer risk in smokers (2). Lung cancer is associated with increased DNA damage in smokers. The authors describe the application of a 96-well plate solid phase extraction and isotope-dilution nanoLC/MS methodology for the determination of N7-(1-hydroxy-3-buten-2-yl) guanine (EB-GII) adducts in the urine samples of smokers. EB-GII is a potential biomarker of 1,3-butadiene exposure, a known human carcinogen found in cigarette smoke. The study demonstrated that EB-GII is associated with smoking status and is a valid biomarker of smoking induced DNA damage. Next, Sliwinski and coworkers provide a comprehensive overview describing the measurement and characterisation of DNA damage and RNA damage in major neuropsychiatric disorders (3). The pathoetiology of disorders such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, etc., is described in relation to both DNA damage processes (mainly oxidatively induced lesion formation) and DNA repair pathways. One of the major themes of the review is that the accumulation of DNA damage in neuronal cells is a contributing factor in the development of neurodegenerative disorders. Increased levels of both nuclear and mitochondrial DNA lesions are associated with many of the disorders. The contents of the Special Issue now turn to the structure, functional biology and mechanisms of the DNA repair proteins responsible for correcting the previously described forms of DNA damage as well as other types of DNA damage. The APE1 repair protein is central to the base excision repair (BER) response to DNA damage and is responsible for correcting apurinic/apyrimidinic (AP) sites in DNA strands. AP sites are non-coding lesions that block RNA and/or DNA polymerases. Wilson and coworkers provide a singular overview of the structure and biological activity of APE1 and APE1 variants in the removal of AP sites (4). APE1 functions as an AP endonuclease, 3′-5′ exonuclease, 3′-phosphodiesterase as well as being involved in nucleotide incision repair. Cells that lack APE1 are not viable and defects in APE1 function provide enhanced sensitivity to alkylating agents and selected chemotherapeutic drugs. In the next report, Delaney and Caffrey carefully delineate and review the relationships between the inhibition of BER proteins, the formation of mutations in BER proteins and the development of cancer (5). Mutations in BER proteins can inactivate their enzymatic activity and lead to many different types of cancer. Mutant BER proteins have reduced capacity to bind to their substrates and thus they demonstrate a decreased enzymatic activity. Another contributing factor to the inhibition of BER proteins is due to the packaging of DNA into chromatin. The histone proteins that comprise the nucleosome core particle of chromatin hinder the accessibility of BER proteins to DNA damage substrates. Next, the subject matter turns to the biological function and characterisation of DNA ligases. DNA ligase enzymes seal SBs (single strand breaks—SSBs or double strand breaks—DSBs) in the phosphodiester backbone of DNA. Tomkinson and coworkers provide a thorough overview of the characteristics and biological functions of the human DNA ligases in relation to cancer development and treatment (6). The overexpression of DNA ligases occurs in cancers resulting in the repair of DSBs and resistance to chemotherapeutics. Current preclinical research is devoted towards developing specific inhibitors towards both DNA ligase I and DNA ligase IV. Next, Glazer and Kaplan give an overview of how hypoxia is inherently associated with tumour microenvironments and how hypoxia suppresses DNA repair overall by inhibiting the fidelity of DNA repair pathways (7). The inhibitory effects of hypoxia on homology directed repair (HDR), non-homologous end joining, mismatch repair, nucleotide excision repair, BER and translesion synthesis are described in detail. Emerging research efforts in this area are focused on the potential of using hypoxia to inhibit BER for the purpose of sensitising cells to oxidising and alkylating agents and to inhibit HDR in order to sensitise cells to PARP inhibitors. Slightly changing the DNA repair inhibition focal point, Sweasy and coworkers describe how somatic mutations in tumours lead to the formation of tumour neoepitopes (8). A targeted immune response against the tumour driven by T cell lymphocytes is initiated from the neoepitopes. Sweasy *et al.* provide an overview of the immune response against tumour cells and the pros and cons of utilising immunotherapies based on checkpoint inhibitors and/or tumour vaccines. Combination therapeutic approaches (immunotherapies + conventional radiation/chemotherapy) are also effective against cancers. However, emerging efforts are focused on understanding how defects in cancer cell DNA repair can help promote an increased immune response to tumour neoepitopes. The next report delineates several important aspects of PARP protein activity in the cell. PARP proteins are some of the most heavily characterised DNA repair pathway proteins in humans. PARP proteins act as DNA damage sensors and they function not only in the detection of DNA damage but also in PARylation (synthesis of poly(ADP-ribosyl) groups that covalently attach to other nuclear accessory proteins and to DNA SB termini). Saparbaev and coworkers comprehensively describe the structure of PARP proteins and the mechanism by which PARP proteins (i.e. PARP1 and PARP2) respond to the presence of SSBs or DSBs by catalyzing the synthesis of poly(ADP-ribosyl) groups (9). After the accessory proteins are PARylated, other proteins are recruited to the site of the SBs for DNA repair. The authors describe the mechanism for how PARP attaches to DNA, how chromatin structure poses restrictions on DNA–protein interactions and how chromatin packaging also hinders accessibility of repair proteins to the site of the damage. PARP has the ability to rotate around the DNA helix while undergoing PARylation; this action promotes chromatin decondensation which allows access to the DNA SBs by the DNA repair proteins. Next, Tell and coworkers initially provide the reader with a critical overview of the established functions of BER proteins in relation to cancer development (10). After this traditional description of BER protein functions is carefully laid out, the authors then proceed to go into an in-depth description of the emerging non-canonical roles of BER proteins, not only in cancer development but in the potential development of new cancer treatments. Researchers are encouraged to think about the BER pathway holistically in terms of cancer biology applications. The authors describe and discuss non-canonical roles and applications of the BER protein pathway in such areas as transcriptional regulation, telomere maintenance, RNA/DNA hybrids processing and the potential implications of BER in personalised medicine for cancer treatment. Zharkov and coworkers close this Special Issue of *Mutagenesis* with an original research contribution that evaluates and demonstrates the functional biological mechanisms of the helix–two-turn–helix (H2TH) structural superfamily of DNA repair proteins (Fpg/Nei) (11). The authors show that the H2TH DNA repair proteins have the capacity to perform the repair of lesions in transcription and homologous recombination bubbles. The enzymatic activity of four H2TH glycosylases (NEIL1, NEIL2, Fpg and Nei) was experimentally evaluated on the excision of oxidatively induced lesions located in single stranded and double stranded oligonucleotides, in DNA bubbles and in displacement loops; the excision of lesions was also evaluated on lesions located at different positions within bubbles. Selected H2TH DNA glycosylases were able to excise lesions from a variety of non-canonical DNA structures. In conclusion, we hope that this Special Issue of *Mutagenesis* will prove to be a valuable resource of inspiration for all researchers delving into the fundamental and emerging aspects of DNA damage and DNA repair in human diseases.

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