DNA

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Editorial

From Mutation and Repair to Therapeutics

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As DNA research has developed, in this Special Issue of *DNA*, we aimed to explore recent advancements, with an emphasis on the DNA damage-induced alteration of cellular functions. Eight articles were published in this Special Issue, which can be broadly divided into the following areas.

- Detection of a DNA lesion;
- Translesion synthesis (TLS);
- Transcriptional bypass of DNA adducts;
- Gut microbiome and human cancer;
- Nucleic-acid-modifying enzymes;
- DNA repair.

Five articles focused on each of the first five topics, and three articles described various aspects of DNA repair. Xu and Zhao reported on the development of an enzyme-linked immunosorbent assay (ELISA)-based technique for detecting mitochondrial DNA–protein cross-links (DPCs) known to form between DNA and mitochondrial transcription factor A (TFAM) in cultured human cells [1]. They prepared model TFAM-DPCs using recombinant human TFAM and an abasic site containing a DNA substrate, isolated them in a high yield on a silica gel column, and then evaluated the microplate, DNA-coating solution, and HRP substrate for the specific and sensitive detection of TFAM-DPCs. They also optimized the mtDNA isolation procedure that eliminates most nuclear DNA. The method was robust enough to detect the different levels of TFAM-DPCs in mtDNA from HEK 293 cells under a variety of biological conditions.

Jung reviewed translesion synthesis carried out via a specific Y-family DNA polymerase known as polymerase η (pol η) [2]. Uniquely, pol η can accurately and efficiently bypass the cyclobutane pyrimidine dimer (CPD). However, many other DNA lesions are also bypassed by pol η. In 2010, X-ray crystallography established the N-terminal catalytic domain of pol η. Subsequently, additional pol η catalytic domain crystal structures were reported, including the ones complexed with an incoming nucleotide and a lesion containing DNA, such as CPD, cisplatin GpG adduct, 8-oxoguanine, 8-oxoadenine, N7-methylguanine, O^6-methylguanine, and hypoxanthine. Although pol η's active site is rigid, which allows only a limited number of conformational changes, several contributing factors to facilitate the lesion bypass have been recognized. These include catalytic metal ions, *syn–anti* conformational equilibrium, tautomerization, and the special roles played by some specific residues of pol η. These factors are discussed in detail in the review.

Wang and co-workers investigated the biological consequence of alkyl phosphotriester (alkyl PTE) adducts, which form at relatively high frequencies and are persistent in mammalian tissues, and yet their effects in mammalian cells have not been examined before [3]. The efficiency and fidelity of transcription in mammalian cells were evaluated to determine how alkyl-PTEs with different alkyl group sizes and stereochemical configurations (SP and RP diastereomers of Me and nPr) may influence them. The investigation revealed that the RP diastereomer of Me- and nPr-PTEs moderately and strongly blocked transcription,

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respectively, whereas the SP diastereomer of the two lesions did not noticeably perturb the transcription efficiency. Interestingly, mutant transcripts were not induced by any of the four alkyl-PTEs. Moreover, pol η promoted transcription across the SP-Me-PTE, but not any of the other three lesions. Other TLS polymerases, including Pol κ, Pol ι, Pol ξ, and REV1, did not change either the transcription bypass efficiency or the mutation frequency for any of the alkyl-PTE lesions. This investigation provided important information on the effects of alkyl-PTE lesions on transcription and the role of Pol η in transcriptional bypassing.

Lu and co-workers reported on the association between DNA damage and the gut microbiome and how it leads to diseases such as cancer [4]. Though, in recent years, we have a better appreciation of the many roles played by the gut microbiota in metabolic and physiological interactions with the host, as they can simulate host endogenous processes, such as inflammatory responses; the full spectrum of these processes are still not well understood. These interactions can be either beneficial to the host or deleterious, and some may even contribute to cancer progression. This review focuses on the molecular mechanism of the gut microbiota's role in human cancer. The key events of carcinogenesis, followed by the current knowledge on host DNA damage attributed to the gut microbiota were summarized, including genotoxic endogenous processes induced by the gut microbiota. The association between specific gut microbiota dysbiosis and different types of cancer was discussed. The authors concluded the article with their viewpoint of future research directions on the relationship between the gut microbiota and cancer development.

Li and co-workers reviewed kinetic studies on a group of nucleic-acid-modifying enzymes from AlkB and TET families [5]. The formation and removal of these genetic and epigenetic biomarkers are related to either methylation or demethylation. The main focus of this review is on the demethylation or oxidative modification facilitated by the 2-oxoglutarate (2-OG)/Fe(II)-dependent AlkB/TET family enzymes. Many of these group of enzymes oxidize 2-OG into succinate and methyl into hydroxymethyl, leading ultimately to the generation of a formaldehyde and demethylated base. AlkB enzyme from *Escherichia coli* and the TET family include many members, but only a few have been kinetically studied. The authors provide a review of the kinetic properties of these enzymes and their alkyl substrates, as well as the future direction of this field.

Three articles relate to DNA repair. Lloyd outlined what we can learn from murine knockouts and human polymorphic variants of the base excision repair (BER) enzymes, NEIL1 and OGG1 [6]. OGG1 and NEIL1 have overlapping substrate specificities in that they both recognize and release the imidazole-ring-fragmented guanine, FapyGua, and 8-oxoguanine. Yet, they have many differences in their range of substrate specificity and how they release bases. In addition, the BER pathways and their protein-binding partners are different as well. Murine models harboring a knockout of Neil1 or Ogg1 have been instrumental in demonstrating additional differences. It is particularly interesting that Ogg1-deficient mice are generally refractory to carcinogenesis, whereas Neil1-deficient mice are more susceptible to developing cancer. The expression of a mitochondrial-targeted human OGG1 in both wild-type and Ogg1-deficient mice helps to overcome the adverse health consequences associated with metabolic syndrome. The author linked these BER enzymes to human diseases and how this knowledge can be applied to treatments. The roles that NEIL1 and OGG1 play in maintaining genomic integrity and human disease susceptibility were compared. For example, inhibitors of OGG1 may be used for treatments of asthma, acute myeloid leukemia, and other diseases.

Cook and Delaney outlined how the BER pathway is modulated by the nucleosome core particle (NCP) and described the structural and dynamic factors that influence the ability of BER enzymes to find and repair DNA damage [7]. Structural characteristics of the NCP, such as nucleobase positioning and occupancy, as well as the factors that impact the dynamic nature of NCPs to increase mobilization of nucleosomal DNA, were explored. They discussed how altering the dynamics of NCPs initiates a domino effect that results in the regulation of BER enzymes.

Li and Vasquez discussed the multi-faceted roles of a key DNA repair protein complex ERCC1-XPF nuclease in processing non-B DNA structures [8]. ERCC1-XPF is a structure-specific endonuclease that participates in a variety of DNA repair processes, including nucleotide excision repair (NER), the repair of DNA interstrand cross-links (ICLs), and DNA double-strand break (DSB) repair via homologous recombination. ERCC1-XPF is also involved in the processing of non-B DNA structures. This article focuses on the processing of alternative DNA structures via ERCC1-XPF.

We hope that these articles provide an overview of this rapidly growing field.

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