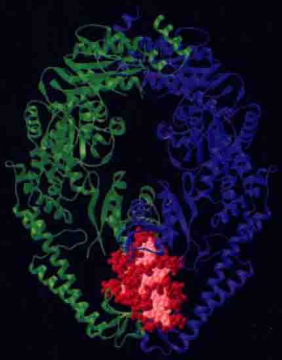
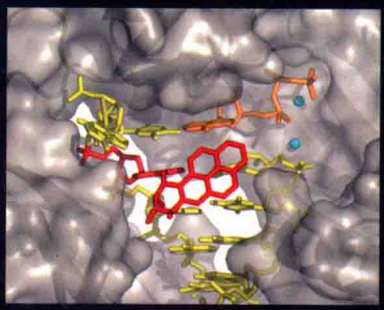


# DNA REPAIR, GENETIC INSTABILITY, AND CANCER



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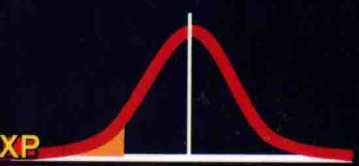

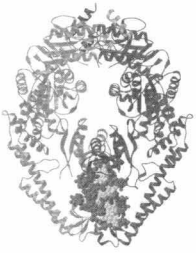

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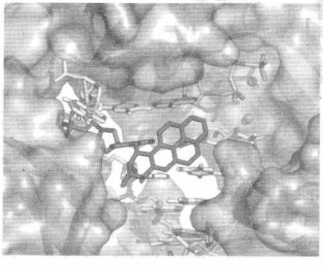


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# DNA REPAIR, GENETIC INSTABILITY, AND CANCER

In memory of Dr. Lawrence (Larry) Grossman,
one of the great pioneers and leaders in the field of DNA repair,
who passed away on January 13, 2006

# Preface

Human DNA is constantly bombarded by endogenous (e.g. reactive oxygen species) and exogenous (UV, ionizing radiation and reactive chemicals) carcinogens. To ensure an accurate passage of genetic information onto daughter cells, cells have evolved elaborate surveillance systems and various DNA repair mechanisms that respond to the harmful stimuli and prevent damaged DNA from being converted to heritable mutations. Over the past 30 years, major frameworks have been established for major DNA repair pathways, including base-excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end-joining (NHEJ).

Since apurinic/apyrimidinic (AP) endonuclease and uracil-DNA glycosylase (UDG), the two enzymes involved in BER were discovered in *Escherichia coli* in the early 1970s, over 20 proteins have been identified as the core and accessory proteins of BER that primarily targets alkylated, deaminated, and oxidized bases, with a certain degree of substrate overlap with other pathways. In contrast, the NER pathway is much more versatile, and is a predominant mechanism protecting cells from UV- and chemical-induced bulky DNA lesions that are often mutagenic. To date, more than 30 genes have been identified that participate in NER. MMR, on the other hand, is an important genome caretaker system. It ensures genomic stability by correcting mismatches generated during DNA replication and

recombination, suppressing homologous recombination, and triggering apoptosis of cells with severe DNA damage. In response to DNA double-strand breaks, the most dangerous lesions, HR may be used to repair the damage. HR plays critical roles in mitotic cells in repairing DNA double-strand breaks and interstrand crosslinks and in restarting replication forks blocked by DNA lesions produced by both reactive intermediates of normal cellular metabolism, exogenous chemicals, and radiation. However, NHEJ is the predominant repair pathway for removing DNA double-strand breaks in mammalian cells. To survive from lesions that block DNA replication, cells have also evolved a pathway that allows for damage tolerance or lesion bypass with high or low fidelity. A key question is how the cell cycle checkpoint machinery detects and signals the presence of damaged DNA that is embedded in millions to billions of normal base pairs. Partial answers come from recent structural and functional studies that reveal atomic details of DNA repair protein and nucleic acid interactions.

The hallmark of cancer is genomic instability that may be initiated from DNA damage and faulty DNA repair systems. The pathogenesis of cancer, which is frequently an environmentally induced disease, reflects the outcome of disrupted balances among diverse biological systems, including those that govern cell growth and proliferation, signal transduction, DNA damage and repair, cell cycle checkpoint and control, and apoptosis in response to environmental insults. Yet, each individual is genetically unique and his or her responses to environmental risk factors or hazards are also unique.

The role of DNA repair in the etiology of cancer has been well illustrated in several hereditary syndromes, in which an inherited defect in DNA repair and related biological processes is associated with extraordinarily high incidence of cancer. For example, patients with xeroderma pigmentosum (XP) have germline mutations in NER genes and have more than 100-fold increased risk of UV-induced skin cancers; patients with hereditary non-polyposis colon cancer (HNPCC) have a defect in MMR due to germline mutations; and patients with Fanconi anemia (FA) appear to be sensitive

to agents that cause DNA-crosslinks and have 500-fold increased risk of developing squamous cell carcinomas of the head and neck.

However, associations between inherited DNA repair defect and risk of cancer have not always been apparent in the general population. In the past 10 years, there has been a growing body of literature that begins to address this important research question at the population level. More recently, the discovery of single nucleotide polymorphisms (SNPs) in DNA repair genes has inspired a wave of association studies, some of which established a genetic basis for a suboptimal repair phenotype in the general population. These findings provide a rationale that by genetic screening for functional SNPs, it may be feasible to identify at-risk populations who can be targeted for primary prevention of cancer that has an etiology of genetically determined variation in DNA repair.

To achieve the goal of eradicating cancer, it is paramount to understand the underlying molecular mechanisms for the maintenance of genetic stability. This book provides a snapshot of our current understanding of DNA damage repair and recent advances in the research of DNA repair, genetic instability and cancer.

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