CHEMICAL REVIEWS

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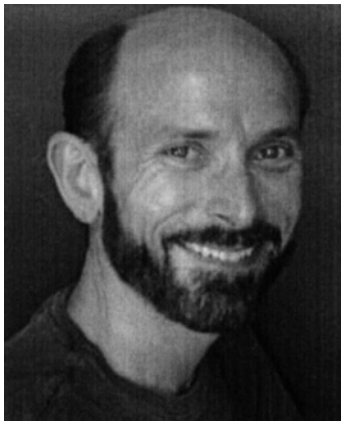
Introduction: DNA Damage and Repair

Hardly more than fifty years have passed since the three-dimensional structure of DNA was elucidated. In essence, this seminal structure in all of biology revealed the linkage between encoded chemical information and genetic inheritance. Because the integrity of any information storage system is only as good as the lifetime of the storage media, it is inevitable that over time the accurate information content of the system degrades. Although the chemical bonds in DNA are exceptionally stable and comparatively unreactive with electrophiles, nucleophiles, and light in the aqueous environment of the cell, the chemical modification of only a single nucleotide in the three billion nucleotide human genome can have a catastrophic effect on the fitness of an individual. Thus, it is imperative that elaborate mechanisms for repairing damaged DNA have evolved which ultimately restore the original chemical information encoded in the genome.

The fact that genetic information is stored in the form of a chemical code makes the field of DNA repair a rich area for chemical investigation, and it presents fundamental problems in biological specificity and control that are immensely interesting. First, enzymes that repair damaged DNA in its many forms must first efficiently recognize the insult in the context of a vast excess of undamaged DNA. Second, once the rare damage site is located, covalent bonds must be broken to ultimately remove the offensive lesion from the genome. In many cases, the bonds that are broken are some of the most stable in biology, requiring high catalytic power from the enzymes facing this challenge. Finally, once the damage is removed, replicative enzymes (DNA polymerases) must frequently restore the original correct coding information by reading the uncorrupted coding information present on the undamaged DNA strand. The types of chemical alterations to the genetic code that must be repaired are diverse and encompass a wide range of chemical reactions: oxidations, hydrolytic deaminations, free radical chemistry, electrophilic additions, photochemical transformations, and nucleophilic substitution reactions.

Although preserving the genomic integrity is of paramount biological importance, DNA repair extends beyond this conceptual framework. Many anticancer drugs act by damaging DNA, thereby arresting cells in the act of DNA replication or chromosome segregation. Thus, in this context, DNA repair is undesirable and drugs that block repair of drug-induced lesions may synergistically enhance the chemotherapeutic effect of some anticancer drugs. A more fundamental question in DNA repair is the importance of deliberate and accidental alterations of the genetic code by DNA repair pathways. Do these alterations play a key role in promoting genetic diversity and, after selection, serve to enhance the fitness of a population?



James T. Stivers was born in Philadelphia, PA, and raised in Anchorage, AK. After pursuing a music degree from Berklee College of Music in Boston and serving as a staff compose.Sr/arranger for the Air Force Band for several years, he received a B.S. in Microbiology and Immunology from the University of Washington in 1987. He obtained his Ph.D. in Biochemistry from Johns Hopkins University in 1992, where he became interested in enzyme catalysis. He received postdoctoral training in heteronuclear NMR and enzymology in the laboratory of Professor Albert Mildvan at Johns Hopkins Medical School, where he was an American Cancer Society postdoctoral fellow from 1993 to 1996. He then joined the faculty of the Center for Advanced Research in Biotechnology in Rockville, MD, as an Assistant Professor in 1996. During the year 2001, he moved his laboratory to the Department of Pharmacology and Molecular Sciences at Johns Hopkins Medical School, where he is now an Associate Professor. Presently, his research focuses on understanding the nature of enzyme catalysis and inhibition for a number of enzymes involved in DNA repair and recombination. When time allows, he still enjoys playing both the classical and electric guitars.

In this thematic issue, a leading contingent of researchers in the field of DNA repair reviews our current understanding of this vibrant area of chemistry and biology. First, the various general types of DNA repair pathways are reviewed. Mishina, Duguid, and He review the role of direct reversal of alkylation damage to DNA bases. Truglio, Croteau, Van Houten, and Kisker then describe the more baroque process of nucleotide excision repair in prokaryotes, while Gillet and Schärer review the analogous process in mammalian systems. Noll, McGregor Mason, and Miller cover the formation and repair of highly toxic DNA interstrand cross-links, and Iyer, Pluciennik, Burdett, and Modrich delve into the complex

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mechanism of repair of base mismatches in DNA. This general overview of repair mechanisms concludes with an examination of the role of homologous recombination in genetic stability by Ishino, Nishino, and Morikawa.

The second topical area reviews the roles of a broad family of mechanistically distinct DNA polymerases. Showalter, Lamarche, Bakhtina, Su, Tang, and Tsai compare and contrast high-fidelity and error-prone DNA polymerases, and Beard and Wilson review the structure and mechanism of pol β, the key polymerase that fills in replacing single-nucleotide gaps in DNA. The role of mitochondrial DNA polymerase γ in repair of the mitochondrial genome is discussed by Graziewicz, Longley, and Copeland, and Schlacher, Pham, Cox, and Goodman provide a critical look at the bacterial DNA polymerase V and its role in SOS damaged-induced mutagenesis. The important area of how polymerases interact with carcinogen-bound DNA is covered by Guengerich, and Rossi, and then Purohit, Brandt, and Bambara delve into how lagging strand polymerases affect genome stability and repair. To round out this section, Saxowsky and Doetsch review the fascinating area of transcription-coupled repair and the impact of RNA polymerase-mediated transcriptional mutagenesis.

We then shift gears with five reviews that cover emerging computational and biophysical methods to understand DNA repair mechanisms. Priyakumar and MacKerell describe computational approaches to understand how enzymes recognize damaged bases by extracting them from the DNA duplex in a remarkable process known as base flipping. Berti and McCann detail how the approach of kinetic isotope effects can be used to study DNA repair reactions and reveal the structure of enzymatic transition states. Biophysical methods for the evaluation of the kinetics and thermodynamics of complex protein−DNA interactions are then reviewed by Bujalowski. Finally, two reviews deal with the mechanistic power of high-resolution structural approaches. Lukin and de los Santos give a comprehensive review of the various structures of damaged DNA as determined by solution NMR methods, and Tomkinson, Vijayakumar, Pascal, and Ellenberger describe the structural and mechanistic insights provided by crystallographic studies of DNA ligases.

Our thematic issue concludes with three reviews that migrate into new and fascinating areas that represent the forefront of DNA repair. Samaranayake, Bujnicki, Carpenter, and Bhagwat review the surprising role of DNA repair in the process of antibody affinity maturation, and O'Brien provides a stimulating overview of how divergent evolution of DNA repair enzymes is related to a fundamental property of enzymes: "catalytic promiscuity". Last, but certainly not least, is a detailed synopsis of DNA repair in plants by Kimura and Sakaguchi with a reflection on the unique problems that must be overcome by plant DNA repair systems.

This thematic issue will serve a valuable role in conveying the fascinating chemical problems inherent to this field, which will in turn foster new questions to be attacked by the next generation of researchers.

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