

Contents

Preface XV

List of Contributors XVII

Part One Chemistry and Biology of DNA Lesions 1

1	Introduction and Perspectives on the Chemistry and Biology of DNA Damage	3
	<i>Nicholas E. Geacintov and Suse Broyde</i>	
1.1	Overview of the Field	3
1.2	DNA Damage—A Constant Threat	4
1.3	DNA Damage and Disease	5
1.3.1	The Inflammatory Response	5
1.3.2	Reactive Oxygen and Nitrogen Species	5
1.3.3	Early Recognition of Environmentally Related Cancers: Polycyclic Aromatic Hydrocarbons	6
1.3.4	Exposure to Environmental Cancer-Causing Substances	6
1.3.5	Aflatoxins	7
1.3.6	Aristolochic Acid	7
1.3.7	Estrogens	8
1.4	DNA Damage and Chemotherapeutic Applications	8
1.5	The Cellular DNA Damage Response (DDR)	9
1.6	Repair Mechanisms that Remove DNA Lesions	10
1.6.1	Repair of Single- and Double-Strand Breaks	10
1.6.2	Alkylating Agents	10
1.6.3	Base Excision Repair	11
1.6.4	Mismatch Excision Repair	11
1.6.5	Nucleotide Excision Repair	11
1.6.6	Translesion Bypass of Unrepaired Lesions by Specialized DNA Polymerases and RNA Polymerases	12
1.7	Relationships between the Chemical, Structural, and Biological Features of DNA Lesions	12
	Acknowledgements	15
	References	15

2	Chemistry of Inflammation and DNA Damage: Biological Impact of Reactive Nitrogen Species	21
	<i>Michael S. DeMott and Peter C. Dedon</i>	
2.1	Introduction	21
2.2	DNA Oxidation and Nitration	23
2.2.1	Spectrum of Guanine Oxidation Products Caused by ONOO ⁻ , ONOOCO ₂ ⁻ , and NO ₂	23
2.2.2	Base Oxidation Products as Biomarkers of Inflammation and Oxidative Stress	25
2.2.3	Charge Transfer as a Determinant of the Location of G Oxidation Products in DNA	25
2.3	DNA Deamination	26
2.3.1	Problem of Oxanine	29
2.3.2	Analytical Methods and Artifacts	29
2.4	2'-Deoxyribose Oxidation	30
2.4.1	Variation of 2'-Deoxyribose Oxidation Chemistry as a Function of the Oxidant	34
2.5	Indirect Base Damage Caused by RNS	35
2.5.1	Malondialdehyde and Related Adducts	37
2.6	Conclusions	38
	Acknowledgements	38
	References	38
3	Oxidatively Generated Damage to Isolated and Cellular DNA	53
	<i>Jean Cadet, Thierry Douki, and Jean-Luc Ravanat</i>	
3.1	Introduction	53
3.1.1	Overview and Summary	53
3.1.2	Overview of Oxidatively Generated DNA Damage	53
3.2	Single Base Damage	55
3.2.1	Singlet Oxygen Oxidation of Guanine	55
3.2.2	Hydroxyl Radical Reactions	58
3.2.2.1	Thymine	58
3.2.2.2	Guanine	60
3.2.2.3	Adenine	62
3.2.3	One-Electron Oxidation of Nucleobases	63
3.2.4	HOCl Acid-Mediated Halogenation of Pyrimidine and Purine Bases	65
3.3	Tandem Base Lesions	66
3.4	Hydroxyl Radical-Mediated 2-Deoxyribose Oxidation Reactions	67
3.4.1	Hydrogen Abstraction at C4': Formation of Cytosine Adducts	67
3.4.2	Hydrogen Atom Abstraction at C5': Formation of Purine 5',8-Cyclonucleosides	68
3.5	Secondary Oxidation Reactions of Bases	70
3.6	Conclusions and Perspectives	71
	Acknowledgements	71
	References	72

4	Role of Free Radical Reactions in the Formation of DNA Damage	81
	<i>Vladimir Shafirovich and Nicholas E. Geacintov</i>	
4.1	Introduction	81
4.2	Importance of Free Radical Reactions with DNA	82
4.2.1	Free Radical Mechanisms: General Considerations	82
4.2.2	Types of Free Radicals and their Reactions with Nucleic Acids	83
4.2.3	Methods for Studying Free Radical Reactions: Laser Flash Photolysis	84
4.2.4	Types of Radical Reactions and Kinetics	85
4.2.5	Examples of DNA Radical Reactions	86
4.2.6	Lifetimes of Free Radicals and Environmental Considerations	88
4.2.7	Reactions of Free Radicals	89
4.3	Mechanisms of Product Formation	91
4.3.1	Reactions of G(-H)· Radicals with Nucleophiles	91
4.3.2	Combinations of G(-H)· and Oxyl Radicals	93
4.3.3	Oxidation of 8-oxoG	97
4.4	Biological Implications	99
	Acknowledgements	100
	References	101
5	DNA Damage Caused by Endogenously Generated Products of Oxidative Stress	105
	<i>Charles G. Knutson and Lawrence J. Marnett</i>	
5.1	Lipid Peroxidation	105
5.2	2'-Deoxyribose Peroxidation	107
5.3	Reactions of MDA and β -Substituted Acroleins with DNA Bases	109
5.4	Stability of M ₁ dG: Hydrolytic Ring-Opening and Reaction with Nucleophiles	112
5.5	Propano Adducts	114
5.6	Etheno Adducts	114
5.7	Mutagenicity of Peroxidation-Derived Adducts	117
5.8	Repair of DNA Damage	121
5.9	Assessment of DNA Damage	123
5.10	Conclusions	126
	Acknowledgements	126
	References	126
6	Polycyclic Aromatic Hydrocarbons: Multiple Metabolic Pathways and the DNA Lesions Formed	131
	<i>Trevor M. Penning</i>	
6.1	Introduction	131
6.2	Radical Cation Pathway	134
6.2.1	Metabolic Activation of PAHs	134
6.2.2	Radical Cation DNA Adducts	135
6.2.3	Limitations of the Radical Cation Pathway	136
6.3	Diol Epoxides	137

- 6.3.1 Metabolic Activation of PAHs 137
- 6.3.2 Diol Epoxide-DNA Adducts 138
- 6.3.3 Limitations of the Diol Epoxide Pathway 140
- 6.4 PAH *o*-Quinones 141
 - 6.4.1 Metabolic Activation of PAH *trans*-Dihydrodiols by AKRs 141
 - 6.4.2 PAH *o*-Quinone-Derived DNA Adducts 142
 - 6.4.2.1 Covalent PAH *o*-Quinone-DNA Adducts 142
 - 6.4.2.2 Oxidative DNA Lesions from PAH *o*-Quinones 144
 - 6.4.3 Limitations of the PAH *o*-Quinone Pathway 146
- 6.5 Future Directions 147
 - Acknowledgements 148
 - References 148

- 7 Aromatic Amines and Heterocyclic Aromatic Amines: From Tobacco Smoke to Food Mutagens 157**
Robert J. Turesky
 - 7.1 Introduction 157
 - 7.2 Exposure and Cancer Epidemiology 157
 - 7.3 Enzymes of Metabolic Activation and Genetic Polymorphisms 159
 - 7.4 Reactivity of *N*-Hydroxy-AAAs and *N*-Hydroxy-HAAs with DNA 161
 - 7.5 Syntheses of AA-DNA and HAA-DNA Adducts 162
 - 7.6 Biological Effects of AA-DNA and HAA-DNA Adducts 162
 - 7.7 Bacterial Mutagenesis 164
 - 7.8 Mammalian Mutagenesis 165
 - 7.9 Mutagenesis in Transgenic Rodents 166
 - 7.10 Genetic Alterations in Oncogenes and Tumor Suppressor Genes 167
 - 7.11 AA-DNA and HAA-DNA Adduct Formation in Experimental Animals and Methods of Detection 168
 - 7.12 AA-DNA and HAA-DNA Adduct Formation in Humans 171
 - 7.13 Future Directions 173
 - Acknowledgements 173
 - References 173

- 8 Genotoxic Estrogen Pathway: Endogenous and Equine Estrogen Hormone Replacement Therapy 185**
Judy L. Bolton and Gregory R.J. Thatcher
 - 8.1 Risks of Estrogen Exposure 185
 - 8.2 Mechanisms of Estrogen Carcinogenesis 187
 - 8.2.1 Hormonal Mechanism 187
 - 8.2.2 Chemical Mechanism 188
 - 8.2.2.1 Oxidative DNA Damage 188
 - 8.2.2.2 DNA Adducts 189
 - 8.2.2.3 Protection against DNA Damage 192
 - 8.3 Estrogen Receptor as a Trojan Horse (Combined Hormonal/Chemical Mechanism) 193

- 8.4 Conclusions and Future Directions 194
 Acknowledgements 194
 References 194

Part Two New Frontiers and Challenges: Understanding Structure–Function Relationships and Biological Activity 201

- 9 Interstrand DNA Cross-Linking 1,N²-Deoxyguanosine Adducts Derived from α,β -Unsaturated Aldehydes: Structure–Function Relationships 203**
Michael P. Stone, Hai Huang, Young-Jin Cho, Hye-Young Kim, Ivan D. Kozekov, Albená Kozekova, Hao Wang, Irina G. Minko, R. Stephen Lloyd, Thomas M. Harris, and Carmelo J. Rizzo
- 9.1 Introduction 203
 9.2 Interstrand Cross-Linking Chemistry of the γ -OH-PdG Adduct (9) 205
 9.3 Interstrand Cross-Linking by the α -CH₃- γ -OH-PdG Adducts Derived from Crotonaldehyde 207
 9.4 Interstrand Cross-Linking by 4-HNE 207
 9.5 Carbinolamine Cross-Links Maintain Watson–Crick Base-Pairing 209
 9.6 Role of DNA Sequence 210
 9.7 Role of Stereochemistry in Modulating Cross-Linking 210
 9.8 Biological Significance 212
 9.9 Conclusions 213
 Acknowledgements 213
 References 213
- 10 Structure–Function Characteristics of Aromatic Amine-DNA Adducts 217**
Bongsup Cho
- 10.1 Introduction 217
 10.2 Major Conformational Motifs 219
 10.2.1 Fully Complementary DNA Duplexes 219
 10.2.2 Other Sequence Contexts 220
 10.3 Conformational Heterogeneity 221
 10.3.1 Sequence Effects on the S/B Conformational Heterogeneity 222
 10.3.2 Conformational Dynamics of the S/B Heterogeneity 224
 10.3.3 Base Sequence Context and Mutagenesis 224
 10.3.4 Dependence of Nucleotide Excision Repair by *E. coli* UvrABC Proteins on Adduct Conformation 225
 10.3.5 Conformational Heterogeneity in Translesion Synthesis 227
 10.3.6 Sequence Effects on the Conformational Stability of SMIs 230
 10.4 Structures of DNA Lesion–DNA Polymerase Complexes 231
 10.5 Conclusions 232
 Acknowledgements 233
 References 233

11	Mechanisms of Base Excision Repair and Nucleotide Excision Repair	239
	<i>Orlando D. Schärer and Arthur J. Campbell</i>	
11.1	General Features of Base Excision and Nucleotide Excision Repair	239
11.2	BER	241
11.2.1	BER Overview—Short-Patch and Long-Patch BER	241
11.2.2	Lesion Recognition by DNA Glycosylases	242
11.2.3	Passing the Baton—Abasic Site Removal and Repair	247
11.3	NER	248
11.3.1	Subpathways of NER: Global Genome and Transcription-Coupled NER	248
11.3.2	Damage Recognition in GG-NER	248
11.3.3	Damage Verification and Lesion Demarcation in NER	251
11.3.4	Dual-Incision and Repair Synthesis in NER	252
11.3.5	Damage Recognition in TC-NER	252
11.4	Conclusions	254
	References	254
12	Recognition and Removal of Bulky DNA Lesions by the Nucleotide Excision Repair System	261
	<i>Yuqin Cai, Konstantin Kropachev, Marina Kolbanovskiy, Alexander Kolbanovskiy, Suse Broyde, Dinshaw J. Patel, and Nicholas E. Geacintov</i>	
12.1	Introduction	261
12.2	Overview of Mammalian NER	261
12.3	Prokaryotic NER	263
12.4	Recognition of Bulky Lesions by Mammalian NER Factors	263
12.5	Bipartite Model of Mammalian NER and the Multipartite Model of Lesion Recognition	264
12.6	DNA Lesions Derived from the Reactions of PAH Diol Epoxides with DNA are Excellent Substrates for Probing the Mechanisms of NER	265
12.7	Multidisciplinary Approach Towards Investigating Structure–Function Relationships in the NER of Bulky PAH-DNA Adducts	268
12.8	Dependence of DNA Adduct Conformations and NER on PAH Topology and Stereochemistry	269
12.8.1	Guanine B[a]P Adducts (Figure 12.3a): Minor Groove and Base-Displaced/Intercalative Conformations	270
12.8.2	Bay Region B[a]P- <i>N</i> ⁶ -Adenine Adducts (Figure 12.3b): Distorting Intercalative Insertions from the Major Groove	271
12.8.3	Fjord Region PAH <i>N</i> ⁶ -Adenine Adducts (Figure 12.3c and d): Minimally Distorting Intercalation from the Major Groove	272
12.8.4	Dependence of NER Efficiencies on the Conformations of the Bay Region B[a]P- <i>N</i> ² -dG Adducts	272
12.8.5	NER Efficiencies: Bay and Fjord Region PAH Diol Epoxide- <i>N</i> ⁶ -dA Adducts	278
12.8.6	Why the <i>trans-anti</i> -B[c]Ph- <i>N</i> ⁶ -dA and Related Fjord Region <i>N</i> ⁶ -dA Adducts do not Destabilize DNA and are Resistant to NER	280

12.9	Dependence of NER of the 10S (+)- <i>trans-anti</i> -B[a]P-N ² -dG Adduct on Base Sequence Context	280
12.9.1	Structural Characteristics of the Identical 10S (+)- <i>trans-anti</i> -B[a]P-N ² -dG Adduct in Different Sequence Contexts	281
12.9.1.1	CG*C and TG*T Sequences	282
12.9.1.2	G6*G7, G6G7*, and I6G7* Sequences	282
12.9.2	Hierarchies of Mammalian NER Recognition Signals	286
12.10	Conclusions	287
	Acknowledgements	289
	References	289
13	Impact of Chemical Adducts on Translesion Synthesis in Replicative and Bypass DNA Polymerases: From Structure to Function	299
	<i>Robert L. Eoff, Martin Egli, and F. Peter Guengerich</i>	
13.1	Introduction	299
13.2	Bypass of Abasic Sites	302
13.3	Lesions Generated by Oxidative Damage to DNA	305
13.4	Exocyclic DNA Adduct Bypass	308
13.5	Alkylated DNA	310
13.6	Polycyclic Aromatic Hydrocarbons and the Effect of Adduct Size upon Polymerase Catalysis	313
13.7	Cyclobutane Pyrimidine Dimers and UV Photoproducts	316
13.8	Inter- and Intrastrand DNA Cross-Links	316
13.9	Conclusions	318
	References	319
14	Elucidating Structure–Function Relationships in Bulky DNA Lesions: From Solution Structures to Polymerases	331
	<i>Suse Broyde, Lihua Wang, Dinshaw J. Patel, and Nicholas E. Geacintov</i>	
14.1	Introduction	331
14.2	Benzo[a]pyrene-Derived DNA Lesions as a Useful Model	331
14.3	Computational Elucidation of the Structural Properties of B[a]P-Derived DNA Lesions in Solution	333
14.4	DNA Polymerase Structure–Function Relationships Elucidated with B[a]P-Derived Lesions	335
14.5	Mechanism of the Nucleotidyl Transfer Reaction	343
14.6	Conclusions and Future Perspectives	345
	Acknowledgements	345
	References	346
15	Translesion Synthesis and Mutagenic Pathways in <i>Escherichia coli</i> Cells	353
	<i>Sushil Chandani and Edward L. Loechler</i>	
15.1	Introduction	353
15.2	Mutagenesis in <i>E. coli</i> has Illuminated Our Understanding of Mutagenesis in General	354

15.3	Why Does <i>E. coli</i> have Three Translesion Synthesis DNA Polymerases? 356
15.4	Overview of the Steps Leading to Translesion Synthesis 358
15.5	Case Studies: AAF-C8-dG and N ² -dG Adducts, Such as +BP 360
15.6	Structure–Function Analysis of Y-Family Pols IV and V of <i>E. coli</i> 362
15.6.1	Structural Basis for a Large versus Small Chimney Opening 366
15.6.2	Roof-Amino Acids and Roof-Neighbor-Amino Acids 368
15.6.3	Interconnected Architecture of the Chimney and Roof Regions 368
15.6.4	dCTP Insertion by Pol IV 369
15.6.5	How Does UmuC(V) Insert dATP? 370
15.6.6	A Cautionary Note about Dpo4 371
15.6.7	Why is Pol IV Efficient at Extension with –BP, but Inefficient with +BP? 372
15.7	Y-Family DNA Polymerase Mechanistic Steps 373
15.8	Structure of B-Family Pol II of <i>E. coli</i> 373
	References 374
16	Insight into the Molecular Mechanism of Translesion DNA Synthesis in Human Cells using Probes with Chemically Defined DNA Lesions 381
	<i>Zvi Livneh</i>
16.1	Introduction 381
16.2	Overview of TLS 382
16.3	Plasmid Model Systems with Defined Lesions for Studying TLS 384
16.4	Gap-Lesion Plasmid Assay for Mammalian TLS 384
16.5	Some Lesions are Bypassed Most Effectively and Most Accurately by Specific Cognate TLS DNA Polymerases 387
16.6	Pivotal Role for Pol ζ in TLS Across a Wide Variety of DNA Lesions 388
16.7	Knocking-Down the Expression of TLS Polymerases using Small Interfering RNA Provides a useful Tool for the Analysis of TLS using the Gapped Plasmid Assay 388
16.8	Evidence that TLS Occurs by Two-Polymerase Mechanisms, in Combinations that Determine the Accuracy of the Process 391
16.9	Conclusions 393
	Acknowledgements 393
	References 394
17	DNA Damage and Transcription Elongation: Consequences and RNA Integrity 399
	<i>Kristian Dreij, John A. Burns, Alexandra Dimitri, Lana Nirenstein, Taissia Noujnykh, and David A. Scicchitano</i>
17.1	Introduction 399
17.2	DNA Repair 400
17.3	Transcription Elongation and DNA Damage 402
17.4	RNA Polymerases: A Brief Overview 402

17.5	RNA Polymerase Elongation Past DNA Damage	407
17.5.1	Abasic Sites, Single-Strand Nicks, and Gaps	407
17.5.2	Oxidative DNA Damage	408
17.5.3	Alkylated Bases in DNA	412
17.5.4	Intrastrand and Interstrand DNA Cross-links	414
17.5.5	“Bulky” DNA Adducts	416
17.6	Conclusions	421
	Acknowledgements	428
	References	429

Index	439
--------------	-----

