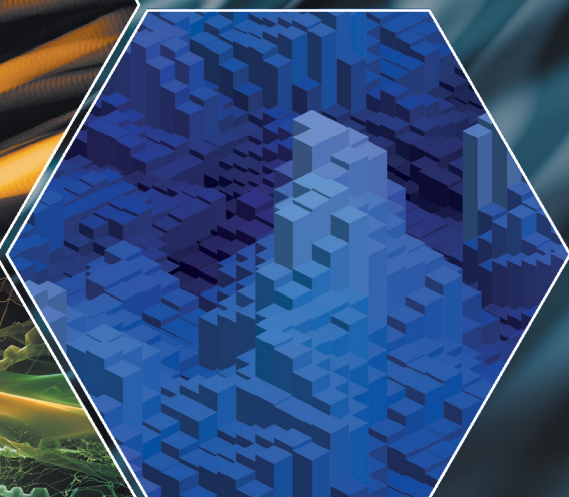
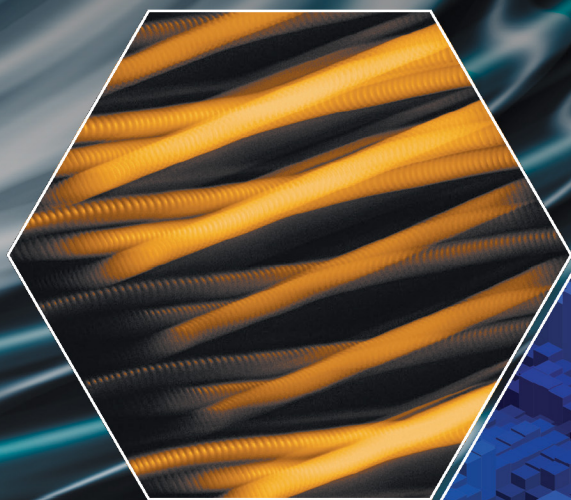


TRANSLATIONAL TOXICOLOGY AND THERAPEUTICS

WINDOWS OF DEVELOPMENTAL
SUSCEPTIBILITY IN
REPRODUCTION
AND CANCER



EDITED BY
MICHAEL D. WATERS
CLAUDE L. HUGHES

WILEY

**Translational Toxicology
and Therapeutics**

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Windows of Developmental
Susceptibility in Reproduction
and Cancer

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Contents

List of Contributors *xix*

Part One Introduction: The Case for Concern about Mutation and Cancer Susceptibility during Critical Windows of Development and the Opportunity to Translate Toxicology into a Therapeutic Discipline 1

1	What Stressors Cause Cancer and When?	3
	<i>Claude L. Hughes and Michael D. Waters</i>	
1.1	Introduction	3
1.1.1	General Information about Cancer	5
1.1.2	Stressors and Adaptive Responses	8
1.2	What Stressors Cause Cancer and When?	8
1.2.1	Mutagenic MOAs	13
1.2.1.1	DNA Repair	14
1.2.2	Epigenetic MOAs	16
1.2.3	Nongenotoxic Carcinogens, ROS, Obesity, Metabolic, Diet, Environment, Immune, Endocrine MOAs	20
1.2.4	Tumor Microenvironment MOAs	25
1.3	Relevance of Circulating Cancer Markers	26
1.4	Potential Cancer Translational Toxicology Therapies	29
1.4.1	Well-Established/Repurposed Pharmaceuticals	31
1.4.2	GRAS/GRASE, Diet, and Nutraceuticals	34
1.4.2.1	Suppression of Cell Proliferation and Induction of Cell Death	35
1.4.2.2	Anti-Inflammatory Effects: Insights from Various Diseases	36
1.4.2.3	Upregulation of Tumor Suppressor MicroRNAs	38
1.4.2.4	Regulation of Oxidative Stress	38
1.4.2.5	Activation of Signal Transduction Pathways	39
1.4.2.6	Mitigating Inherited Deleterious Mutations	40
1.4.2.7	Mitigating Adverse Epigenetic States	42

1.4.2.8	Paradigm for Study of Cancer Chemoprevention	43
1.5	Modeling and the Future	47
	References	51
2	What Mutagenic Events Contribute to Human Cancer and Genetic Disease?	61
	<i>Michael D. Waters</i>	
2.1	Introduction	61
2.1.1	Childhood Cancer, Developmental Defects, and Adverse Reproductive Outcomes	62
2.1.2	Newborn Screening for Genetic Disease	62
2.1.3	Diagnosis of Genetic Disease	63
2.1.4	Familial and Sporadic Cancer	65
2.2	Genetic Damage from Environmental Agents	67
2.3	Testing for Mutagenicity and Carcinogenicity	71
2.4	Predictive Toxicogenomics for Carcinogenicity	73
2.5	Germ Line Mutagenicity and Screening Tests	76
2.6	Reproductive Toxicology Assays in the Assessment of Heritable Effects	80
2.6.1	Segmented Reproductive Toxicity Study Designs	80
2.6.2	Continuous Cycle Designs	81
2.6.2.1	One-Generation Toxicity Study	81
2.6.2.2	Repeat Dose Toxicity Studies	82
2.7	Assays in Need of Further Development or Validation	82
2.7.1	Transgenic Rodent Gene Mutation Reporter Assay	82
2.7.2	Expanded Simple Tandem Repeat Assay	84
2.7.3	Spermatid Micronucleus (MN) Assay	85
2.7.4	Sperm Comet Assay	86
2.7.5	Standardization of Sperm Chromatin Quality Assays	86
2.8	New Technologies	87
2.8.1	Copy Number Variants and Human Genetic Disease	87
2.8.2	Next-Generation Whole Genome Sequencing	88
2.8.3	High-Throughput Analysis of Egg Aneuploidy in <i>C. elegans</i> , and Other Alternative Assay Systems	90
2.9	Endpoints Most Relevant to Human Genetic Risk	91
2.10	Worldwide Regulatory Requirements for Germ Cell Testing	94
2.11	Conclusion	95
	Acknowledgments	96
	References	96
3	Developmental Origins of Cancer	111
	<i>Suryanarayana V. Vulimiri and John M. Rogers</i>	
3.1	Introduction	111

3.2	Current Trends in Childhood Cancer	112
3.3	Potential Mechanisms of Prenatal Cancer Induction	113
3.4	Ontogeny of Xenobiotic Metabolizing Enzymes and DNA Repair Systems	113
3.5	The Developmental Origins of Health and Disease (DOHaD) Theory	115
3.6	Epigenetic Regulation during Development	115
3.6.1	Critical Periods for Epigenetic Regulation	116
3.7	Mechanisms of Cancer in Offspring from Paternal Exposures	117
3.8	Parental Exposures Associated with Cancer in Offspring	118
3.8.1	Radiation	118
3.8.2	Diethylstilbestrol	119
3.8.3	Tobacco Smoke	120
3.8.4	Pesticides	122
3.8.5	Arsenic	123
3.9	Models for the Developmental Origins of Selected Cancers	124
3.9.1	Breast Cancer	124
3.9.2	Leukemia	127
3.10	Public Health Agencies' Views on Prenatal Exposures and Cancer Risk	129
3.10.1	The United States Environmental Protection Agency (US EPA)	129
3.10.2	The California Environmental Protection Agency (CalEPA)	131
3.10.3	Washington State Department of Ecology (WA DoE)	133
3.11	Conclusions	134
	Acknowledgment	135
	References	135
4	The Mechanistic Basis of Cancer Prevention	147
	<i>Bernard W. Stewart</i>	
4.1	Introduction	147
4.2	A Mechanistic Approach	147
4.2.1	Specifying Carcinogens	148
4.2.2	Cancer Risk Factors Without Carcinogen Specification	148
4.3	Preventing Cancer Attributable to Known Carcinogens	149
4.3.1	Involuntary Exposure	149
4.3.1.1	Infectious Agents	149
4.3.1.2	Occupation	150
4.3.1.3	Drugs	151
4.3.1.4	Pollution	152
4.3.1.5	Dietary Carcinogens	152
4.3.2	Tobacco Smoking	153
4.3.2.1	Measures to Limit Availability and Promotion	154
4.3.2.2	Product Labeling, Health Warnings, and Usage Restrictions	154

- 4.3.2.3 Smoking Cessation 155
- 4.3.3 Alcohol Drinking 155
- 4.3.4 Solar and Ultraviolet Radiation 156
- 4.4 Prevention Involving Complex Risk Factors 157
- 4.4.1 Workplace Exposures 157
- 4.4.2 Diet and Overweight/Obesity 157
- 4.5 Prevention Independent of Causative Agents or Risk Factors 158
- 4.5.1 Screening 158
- 4.5.2 Chemoprevention 159
- 4.6 Conclusion 160
- References 160

Part Two Exposures that Could Alter the Risk of Cancer Occurrence, and Impact Its Indolent or Aggressive Behavior and Progression Over Time 171

5 Diet Factors in Cancer Risk 173

Lynnette R. Ferguson

- 5.1 Introduction 173
- 5.2 Obesity 174
- 5.3 Macronutrients 175
- 5.3.1 Protein 176
- 5.3.2 Lipids 177
- 5.3.3 Carbohydrates 178
- 5.4 Micronutrients 181
- 5.4.1 Vitamins 181
- 5.4.2 Minerals 184
- 5.5 Phytochemicals 184
- 5.5.1 Phytoestrogens 185
- 5.5.2 Other Phytochemicals 186
- 5.6 Conclusions 188
- References 188

6 Voluntary Exposures: Natural Herbs, Supplements, and Substances of Abuse – What Evidence Distinguishes Therapeutic from Adverse Responses? 199

Eli P. Crapper, Kylie Wasser, Katelyn J. Foster, and Warren G. Foster

- 6.1 Introduction 199
- 6.1.1 Alcohol 200
- 6.1.2 Cigarette Smoking 201
- 6.1.3 Herbs and Supplements 202
- 6.1.3.1 Melatonin 202

- 6.1.3.2 Resveratrol 204
- 6.1.3.3 Dong Quai 205
- 6.1.3.4 Eleutherococcus 206
- 6.1.3.5 Saw Palmetto 206
- 6.1.3.6 Stinging Nettle 207
- 6.2 Summary and Conclusions 207
- References 207

- 7 Voluntary Exposures: Pharmaceutical Chemicals in Prescription and Over-the-Counter Drugs – Passing the Testing Gauntlet 213**
Ronald D. Snyder
- 7.1 Introduction 213
- 7.2 Testing of New Drug Entities for Genotoxicity 214
- 7.3 Relationship between Genotoxicity Testing and Rodent Carcinogenicity 217
- 7.4 Can Drug-Induced Human Cancer Be Predicted? 218
- 7.5 What Can Rodent Carcinogenicity Tell Us about Human Cancer Risk? 220
- 7.6 Genotoxicity Prediction Using “Traditional” *In Silico* Approaches 222
- 7.7 Covalent versus Noncovalent DNA Interaction 223
- 7.8 Use of New Technologies to Predict Toxicity and Cancer Risk: High-Throughput Methods 224
- 7.9 Transcriptomics 225
- 7.10 Single-Nucleotide Polymorphisms (SNPs) 226
- 7.11 Conclusions 227
- Appendix A 228
- References 253

- 8 Children’s and Adult Involuntary and Occupational Exposures and Cancer 259**
Annamaria Colacci and Monica Vaccari
- 8.1 Introduction 259
- 8.2 Occupational Exposures and Cancer 262
- 8.2.1 Occupational Cancer in the Twenty-First Century 262
- 8.2.2 Past and Present Occupational Exposure to Asbestos 263
- 8.2.3 Toxicology of Fibers: What We Have Learned from the Asbestos Lesson 265
- 8.2.3.1 Mechanism and Mode of Action of Asbestos and Asbestos-Like Fibers in Carcinogenesis: The Role of Inflammation and Immune System to Sustain the Cancer Process 268
- 8.2.4 Occupational Exposures and Rare Tumors 270
- 8.3 Environmental Exposures and Cancer 271

- 8.3.1 Environmental Exposures and Disease: Is This the Pandemic of the Twenty-First Century? 271
- 8.3.2 The Complexity of Environmental Exposures 272
- 8.3.3 Environmental Impact on Early Stages of Life: Are Our Children at Risk? 274
- 8.3.4 Environmental Endocrine Disruptors: The Steps Set Out to Recover Our Stolen Future 277
- 8.3.5 From Occupational to Environmental Exposures: Asbestos and Other Chemicals of Concern 279
 - 8.3.5.1 Asbestos 279
 - 8.3.5.2 Arsenic and Arsenic Compounds 280
 - 8.3.5.3 Phthalates 282
 - 8.3.5.4 Pesticides 283
 - 8.3.5.5 Mycotoxins 286
- 8.3.6 Air Pollution and Airborne Particulate Matter: The Paradigmatic Example of Environmental Mixtures 288
 - 8.3.6.1 Characteristics of PM and PM Exposures 289
 - 8.3.6.2 PM Exposures and Cancer 291
 - 8.3.6.3 Possible Mechanisms of PM Toxicity 293
 - 8.3.6.4 The Role of PM Exposures in the Fetal Origin of the Disease 294
- 8.4 Conclusions and Future Perspectives 296
 - References 299

Part Three Gene–Environment Interactions 317

- 9 Ethnicity, Geographic Location, and Cancer 319**
Fengyu Zhang
 - 9.1 Introduction 319
 - 9.2 Classification of Cancer 320
 - 9.2.1 Classification by Histology 320
 - 9.2.2 Classification by Primary Location 322
 - 9.3 Ethnicity and Cancer 323
 - 9.3.1 Cancer Death and Incidence 323
 - 9.3.2 Site-Specific Cancer Incidence 326
 - 9.3.3 Site-Specific Cancer Incidence between the United States and China 328
 - 9.4 Geographic Location and Cancer 331
 - 9.4.1 Mapping Human Diseases to Geographic Location 331
 - 9.4.2 Geographic Variation and Cancer in the United States 332
 - 9.5 Ethnicity, Geographic Location, and Lung Cancer 334
 - 9.5.1 Ethnic Differences 334
 - 9.5.2 Geographic Variation 335

9.5.3	Individual Risk Factors	335
9.6	Common Cancers in China	338
9.6.1	Liver Cancer	339
9.6.1.1	Geographic Variation	339
9.6.1.2	Urban Residence and Sex	340
9.6.1.3	Hepatitis B Virus Infection	340
9.6.1.4	Familial Aggregation and Genetic Variants	341
9.6.2	Gastric Cancer	342
9.6.2.1	<i>H. pylori</i>	342
9.6.2.2	Familial Aggregation	343
9.6.2.3	Genetic Susceptibility Factors	343
9.6.3	Esophageal Cancer	344
9.6.3.1	Geographic Variation	344
9.6.3.2	Viral Infections	344
9.6.3.3	Familial Aggregation	345
9.6.3.4	Genetic Susceptibility Factors	345
9.6.4	Lung Cancer	346
9.6.5	Genetic Susceptibility Factors	347
9.6.6	Cervical Cancer	348
9.7	Cancer Risk Factors and Prevention	348
9.7.1	Environmental Chemical Exposure	348
9.7.2	Infectious Agents	349
9.7.3	Psychosocial Stress and Social Network	349
9.7.4	The Developmental Origin of Adult-Onset Cancer	350
9.7.5	Cancer Prevention and Intervention	351
	References	353
10	Dietary/Supplemental Interventions and Personal Dietary Preferences for Cancer: Translational Toxicology Therapeutic Portfolio for Cancer Risk Reduction	363
	<i>Sandeep Kaur, Elaine Trujillo, and Harold Seifried</i>	
10.1	Introduction	363
10.2	Gene Expression and Epigenetics	364
10.3	Environmental Lifestyle Factors Affecting Cancer Prevention and Risk	366
10.3.1	Obesity	366
10.3.2	Weight Loss	368
10.3.3	Physical Activity	369
10.4	Dietary Patterns	370
10.5	Complementary and Integrative Oncology Interventions/Restorative Therapeutics	373
10.6	Special and Alternative Diets	377
10.7	Popular Anticancer Diets	378

- 10.7.1 Macrobiotic Diet 378
- 10.7.2 The Ketogenic Diet 382
- 10.7.3 Fasting Diet 383
- 10.8 Conclusion 384
- Acknowledgment 384
- References 385

11 Social Determinants of Health and the Environmental Exposures: A Promising Partnership 395

Lauren Fordyce, David Berrigan, and Shobha Srinivasan

- 11.1 Introduction 395
- 11.1.1 Conceptual Model 397
- 11.1.2 Difference versus Disparity 398
- 11.2 Social Determinants of Health 399
- 11.2.1 Race/Ethnicity 399
- 11.2.2 Social Determinants of Health: “Place” and Its Correlates 402
- 11.2.3 Gender and Sexuality 405
- 11.3 Conclusions: Social Determinants of Health and Windows of Susceptibility 407
- Acknowledgments 408
- References 408

Part Four Categorical and Pleiotropic Nonmutagenic Modes of Action of Toxicants: Causality 415

12 Bisphenol A and Nongenotoxic Drivers of Cancer 417

Natalie R. Gassman and Samuel H. Wilson

- 12.1 Introduction 417
- 12.2 Dosing 420
- 12.3 Receptor-mediated Signaling 421
- 12.4 Epigenetic Reprogramming 422
- 12.5 Oxidative stress 424
- 12.6 Inflammation and Immune Response 425
- 12.7 BPA-Induced Carcinogenesis 426
- 12.8 Fresh Opportunities in BPA Research 428
- References 429

13 Toxicoeugenetics and Effects on Life Course Disease Susceptibility 439

Luke Montrose, Jaclyn M. Goodrich, and Dana C. Dolinoy

- 13.1 Introduction to the Field of Toxicoeugenetics 439
- 13.1.1 The Epigenome 440

- 13.1.2 Epigenetic Marks are Heritable and Reversible 440
- 13.1.3 DNA Methylation 441
- 13.1.4 Histone Modifications and Chromatin Packaging 442
- 13.1.5 Noncoding RNAs 443
- 13.1.6 Key Windows for Exposure-Related Epigenetic Changes 443
- 13.1.7 Evaluation of Environmentally Induced Epigenetic Changes in Animal Models and Humans 444
- 13.2 Exposures that Influence the Epigenome 444
 - 13.2.1 Air Pollution 445
 - 13.2.2 Metals 447
 - 13.2.3 Endocrine Disrupting Chemicals (EDCs) 448
 - 13.2.4 Diet 451
 - 13.2.5 Stress 453
- 13.3 Intergenerational Exposures and Epigenetic Effects 454
- 13.4 Special Considerations and Future Directions for the Field of Toxicopigenetics 456
 - 13.4.1 Tissue Specificity 456
 - 13.4.2 The Dynamic Nature of DNA Methylation 458
- 13.5 Future Directions 459
- 13.6 Conclusions 460
 - Acknowledgments 461
 - References 461

- 14 Tumor-Promoting/Associated Inflammation and the Microenvironment: A State of the Science and New Horizons 473**
William H. Bisson, Amedeo Amedei, Lorenzo Memeo, Stefano Forte, and Dean W. Felsher
 - 14.1 Introduction 473
 - 14.2 The Immune System 475
 - 14.2.1 Innate Immune Response 475
 - 14.2.2 Adaptive Immune Response 478
 - 14.3 Prioritized Chemicals 482
 - 14.3.1 Bisphenol A 482
 - 14.3.2 Polybrominated Diphenyl Ethers 483
 - 14.3.3 4-Nonylphenol 485
 - 14.3.4 Atrazine 485
 - 14.3.5 Phthalates 486
 - 14.4 Experimental Models of Carcinogenesis through Inflammation and Immune System Deregulation 487
 - 14.5 Antioxidants and Translational Opportunities 493
 - 14.6 Tumor Control of the Microenvironment 495
 - Acknowledgments 497
 - References 497

- 15 Metabolic Dysregulation in Environmental Carcinogenesis and Toxicology 511**
R. Brooks Robey
- 15.1 Introduction 511
- 15.2 Metabolic Reprogramming and Dysregulation in Cancer 513
- 15.2.1 Carbohydrate Metabolism in Cancer 515
- 15.2.2 Lipid Metabolism in Cancer 519
- 15.2.3 Protein Metabolism in Cancer 521
- 15.3 Moonlighting Functions 523
- 15.4 Cancer Metabolism in Context 523
- 15.4.1 The Gestalt of Intermediary Metabolism 523
- 15.4.2 Cancer Tissues, Cells, and Organelles as Open Systems 527
- 15.4.3 The Endosymbiotic Nature of Cancer 527
- 15.4.4 Catabolic and Anabolic Support of Cell Proliferation 528
- 15.4.5 Cancer Heterogeneity 529
- 15.4.6 Phenotypic Relationships between Cancer Cells and Their Parental Cell Origins 532
- 15.4.7 Evolutionary Perspectives of Metabolic Fitness and Selection in Cancer Development 533
- 15.5 Dual Roles for Metabolism in Both the Generation and Mitigation of Cellular Stress 536
- 15.5.1 Metabolism and Oxidative Stress 537
- 15.5.2 Metabolism and Hypoxic Stress 539
- 15.5.3 Nutritional Stress and Metabolism 539
- 15.5.4 Metabolism and Physical Stress 540
- 15.5.5 Metabolism and Other Forms of Cellular Stress 541
- 15.6 Models of Carcinogenesis 541
- 15.6.1 Traditional Multistage Models of Cancer Development 542
- 15.6.2 Role of Replicative Mutagenesis in Cancer Development 543
- 15.6.3 Acquired Mismatch Model of Carcinogenesis 543
- 15.7 Potential Metabolic Targets for Environmental Exposures 546
- 15.7.1 Conceptual Overview of Potential Metabolic Targets 546
- 15.7.2 Identification of Key Targetable Contributors to Metabolic Dysregulation and Selection 549
- 15.7.2.1 Glycolysis 555
- 15.7.2.2 Lipogenesis, Lipolysis, and the PPP 555
- 15.7.2.3 Citric Acid Cycle 556
- 15.7.2.4 Organizational or Compartmental Targets 556
- 15.7.2.5 Metabolite Transport Mechanisms 557
- 15.7.2.6 Signal Transduction Effectors 558
- 15.8 Metabolic Changes Associated with Exposures to Selected Agents 559

- 15.8.1 Selected Agents Classified by the World Health Organization's International Agency for Research on Cancer (IARC) 559
 - 15.8.1.1 IARC Group 1 (Carcinogenic to Humans) 560
 - 15.8.1.2 IARC Group 2A (Probably Carcinogenic to Humans) 564
 - 15.8.1.3 IARC Group 2B (Possibly Carcinogenic to Humans) 565
 - 15.8.1.4 Other Agents 565
- 15.8.2 Environmentally Relevant Combinatorial Exposures 567
 - 15.8.2.1 Occupational and Common Environmental Exposures 567
 - 15.8.2.2 Environmentally Relevant Low-Dose Combinatorial Exposures 568
 - 15.8.2.3 The Halifax Project 570
- 15.9 A Conceptual Overview of Traditional and Emerging Toxicological Approaches to the Problem of Cancer Metabolism: Implications for Future Research 571
 - 15.9.1 General Experimental Considerations in the Study of Metabolism *In Vitro* 571
 - 15.9.2 Systems Biology and Current Approaches to *In Vitro* Toxicology Screening 573
- 15.10 The Nosology of Cancer and Cancer Development 577
- 15.11 Discussion 579
 - Acknowledgments 583
 - References 583

Part Five Biomarkers for Detecting Premalignant Effects and Responses to Protective Therapies during Critical Windows of Development 607

- 16 Circulating Molecular and Cellular Biomarkers in Cancer 609**
Ilaria Chiodi, A. Ivana Scovassi, and Chiara Mondello
- 16.1 Introduction 609
- 16.2 Proteins in Body Fluids: Potential Biomarkers 610
 - 16.2.1 Diagnostic Protein Biomarkers 612
 - 16.2.2 Prognostic Protein Biomarkers 613
 - 16.2.3 Protein Biomarkers of Drug Response 615
- 16.3 Circulating Cell-Free Nucleic Acids 615
 - 16.3.1 Circulating Cell-Free Tumor DNA 616
 - 16.3.1.1 Cf-DNA Integrity, Microsatellite Instability, and LOH 617
 - 16.3.1.2 Tumor-Specific Genetic Alterations 617
 - 16.3.1.3 Tumor Genetic Alterations and Therapy Resistance 619
 - 16.3.1.4 Tumor Epigenetic Alterations: DNA Methylation 620
 - 16.3.2 Circulating Cell-Free RNA 621
 - 16.3.2.1 Circulating Cell-Free microRNA 621
- 16.4 Extracellular Vesicles: General Features 624

- 16.4.1 Classification of EVs 624
- 16.4.2 EVs and Cancer 625
- 16.4.3 EVs as Mediators of Cell-To-Cell Communication 627
- 16.5 Circulating Tumor Cells 628
- 16.5.1 Two-Step Processing of Blood Samples: Enrichment and Identification of Circulating Tumor Cells 628
 - 16.5.1.1 CTC Number as a Cancer Biomarker 630
 - 16.5.2 Characterization of CTCs 630
 - 16.5.2.1 Molecular Characterization of CTCs 630
 - 16.5.2.2 Functional Characterization of CTCs 632
 - 16.5.3 Single CTCs *versus* CTC Clusters 634
 - 16.5.4 In Hiding Before Getting Home, the Long Journey of CTCs 635
- 16.6 Conclusions 635
- References 637

- 17 Global Profiling Platforms and Data Integration to Inform Systems Biology and Translational Toxicology 657**
Barbara A. Wetmore
 - 17.1 Introduction 657
 - 17.2 Global Omics Profiling Platforms 659
 - 17.2.1 Genomics 659
 - 17.2.2 Epigenomics 661
 - 17.2.3 Transcriptomics 662
 - 17.2.4 Proteomics 665
 - 17.2.5 Metabolomics 668
 - 17.3 High-Throughput Bioactivity Profiling 669
 - 17.3.1 High-Throughput Bioactivity and Toxicity Screening 669
 - 17.3.2 *In Vitro*–*In Vivo* Extrapolation 671
 - 17.4 Biomarkers 672
 - 17.5 Exposomics 673
 - 17.6 Bioinformatics to Support and Data Integration and Multiomics Efforts 674
 - 17.7 Data Integration: Multiomics and High-Dimensional Biology Efforts 676
 - 17.8 Conclusion 679
 - References 679

- 18 Developing a Translational Toxicology Therapeutic Portfolio for Cancer Risk Reduction 691**
Rebecca Johnson and David Kerr
 - 18.1 Introduction 691
 - 18.2 The Identification of Novel Predictors of Adverse Events 693
 - 18.2.1 Candidate Gene Studies 693
 - 18.2.2 Genome-wide Associations 694

18.2.3	Next-Generation Sequencing	695
18.3	Proof of Principle Toxgnostics	696
18.4	Proposed Protocol	698
18.4.1	Integration within Randomized Control Trials	698
18.4.2	Biobanking and Future-Proofing Samples	699
18.4.3	Data Protection and Full Consent	702
18.4.4	The Need for a Collaborative Approach	703
18.4.5	Open Access to Results	704
18.4.6	Translation from Bench to Bedside	705
18.5	Fiscal Matters	706
18.6	The Future of Toxgnostics	706
	References	707
19	Ethical Considerations in Developing Strategies for Protecting Fetuses, Neonates, Children, and Adolescents from Exposures to Hazardous Environmental Agents	711
	<i>David B. Resnik and Melissa J. Mills</i>	
19.1	Introduction	711
19.2	What Is Ethics?	712
19.2.1	Some Fundamental Ethical Values	712
19.2.1.1	Benefits and Costs	712
19.2.1.2	Individual Rights and Responsibilities	713
19.2.1.3	Justice	713
19.2.2	Value Conflicts and Ethical Decision-Making	713
19.3	Ethical Considerations for Strategies Used to Protect Fetuses, Neonates, Children, and Adolescents from Exposures to Harmful Environmental Agents	715
19.3.1	Education	715
19.3.2	Testing/Screening/Monitoring	717
19.3.3	Worker Protection	720
19.3.4	Government Regulation	722
19.3.5	Taxation	725
19.3.6	Civil Liability	726
19.3.7	Criminal Liability	729
19.4	Research with Human Participants	730
19.4.1	Return of Individualized Research Results	732
19.4.2	Protecting Privacy and Confidentiality	733
19.4.3	Interventional Studies	734
19.4.4	Intentional Exposure Studies	736
19.4.5	Protecting Vulnerable Participants	739
19.5	Conclusion	742
	References	742
	Index	751

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Part One

Introduction: The Case for Concern about Mutation and Cancer Susceptibility during Critical Windows of Development and the Opportunity to Translate Toxicology into a Therapeutic Discipline

1

What Stressors Cause Cancer and When?

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1.1 Introduction

Translational biomedical research seeks to move laboratory findings based on models (*in silico*, *in vitro*, and *in vivo*) into human clinical trials to more expeditiously develop specific therapeutics, and then back again to the laboratory to inform future discovery [1]. From the background of developmental toxicology, it is well known that toxicant exposures may affect critical events in reproductive development, ranging from early primordial germ cell determination to gonadal differentiation, gametogenesis, external genitalia, or signaling events regulating sexual behavior. Translational genetic toxicology takes advantage of this developmental perspective to assess potential germ line mutagenesis or to study the potential for cancer in the fetus or offspring or the adult as the result of environmental exposures. Translational toxicology must strive to identify applicable therapeutics that can safely and effectively identify and help to mitigate potential harm from natural as well as anthropogenic environmental exposures.

Human exposures to chemicals, physical agents, and social factors are inevitable, thus the human fetus and the adult are subject to exposures and effects that can have lifelong consequences. Particularly, during dynamic developmental intervals described as “critical windows of susceptibility,” exposures may have robust and durable effects that drive long-term health outcomes, including metabolism, functional status of organ systems, and cancer risks [2]. These same dynamic developmental intervals should be seen as “critical windows of responsivity” during which favorable/protective interventions should also be highly impactful offering potential durable reduction in

risks of multiple adverse health outcomes, including cancers. To reduce the lifelong occurrence of preventable cancers, timely protective interventions during “critical windows” should include not only minimization of untoward voluntary exposures and substances of abuse but also active use of protective generally recognized as safe (GRAS) interventions/therapies, including nutritional, dietary supplementation, or well-established/repurposed and/or generally recognized as safe and effective (GRASE) pharmaceutical drugs.

This introductory chapter will promote the elucidation of cell stage, life stage, and lifestyle knowledge of specific cellular and molecular targets of known developmental toxicants, develop a systematic integrated approach to the identification of mutagenic and reproductive toxicants, and discuss sensitive, specific, and predictive animal models, to include minimally invasive surrogate markers, and/or *in vitro* tests to assess reproductive system function during embryonic, postnatal, and adult life. It will argue that integrated testing strategies will be required to account for the many mechanisms associated with development that occur *in vivo*. A key organizing principle used throughout this book is to consider how exposures that incur risk or other exposures/life events that may reduce risk during particular windows of susceptibility/developmental transitions, and thereby impact cancer occurrence.

In consideration of any cause–effect relationship, typically one thinks of the simple questions: Who, what, where, when, and how? Admittedly, “How?” questions are generally the most difficult because that understanding is a synthesis of potentially causal pathways. We aim to consider that the “Who?” and “When?” questions could be seen as people being exposed at different intervals across their respective life spans. Thus, in addition to information regarding what exposures occur that influence cancer occurrence, what is and is not known about exposures to those agents during life span intervals such as childhood, adolescence, across the broader life span, and/or late in life? Assessment of such timing of exposure with cancer outcomes seems to be a critical element if we aim to develop protective interventional strategies. In other words, whether we aim to reduce exposures or advocate protective lifestyle or therapeutic interventions, we must know when those interventions would most effectively impact later cancer outcomes.

Although there are differences between human development and that of laboratory animal models, developmental models have been extremely useful in assessing risks for key human reproductive and developmental processes. Some of these models will be discussed in Chapters 2 and 3. However, such systems have not been fully integrated with models to assess germ line mutagenesis or to study the potential for cancer in the fetus or offspring as the result of environmental exposures. Again, Chapters 2 and 3 will address current proposals for experimental animal test system integration.

To delve into the impact of exposures during “windows of susceptibility/responsivity,” we must take into account the unique susceptibilities of the fetus.

Relatively, new information suggests that some widely held notions relevant to fetal exposures are incorrect [3]. Thus, we now know that amniotic fluid can be reabsorbed into the fetal circulation by fetal swallowing as well as via the fetal intramembranous pathway. The latter pathway is thought to be the most important mechanism for the resorption of toxicants, such as ethanol, into the fetal circulation [4]. Together with swallowing, this is a recycling system, through which toxic substances are excreted into the amniotic fluid and reabsorbed into the fetal circulation, thus extending the duration of each exposure [5,6]. This and other information relevant to fetal exposure *in utero* will be discussed in Chapter 8.

1.1.1 General Information about Cancer

Each year the American Cancer Society estimates the number of new cancer cases and deaths that will occur in the United States that year. In 2016, a total of 1,685,210 new cancer cases were expected to be diagnosed and about 595,690 cancer deaths were projected to occur in the United States [7]. Among children up to 14 years of age, an estimated 10,380 new cancer cases were expected to occur in 2016.

Population-based cancer registration began in the United States in 1975. Since then, childhood cancer incidence rates have increased by 0.6% per year. In 2016, 1250 cancer deaths were expected to occur among children. Cancer is the second leading cause of death in children ages 1–14 years, exceeded only by accidents. Childhood cancer death rates declined a total of 66% from 1969 (6.5 per 100,000) to 2012 (2.2 per 100,000). According to the American Society, this was largely due to improvements in treatment and high rates of participation in clinical trials. From 2003 to 2012, the rate of cancer-caused deaths in children declined by 1.3% per year.

Siegel *et al.* [8] reported that during the period 2006–2010, the then most recent 5 years for which there were data, the delay-adjusted cancer incidence rates declined by 0.6% per year in men and were stable in women. At the same time, cancer death rates decreased by 1.8% per year in men and by 1.4% per year in women. The rate of combined cancer deaths per 100,000 populations has declined continuously for two decades, from a peak of 215.1 in 1991 to 171.8 in 2010. The 20% decline during this time period equates to the avoidance of 1,340,400 cancer deaths (952,700 among men and 387,700 among women). Siegel *et al.* reported that the magnitude of the decline in cancer death rates varies substantially by age, race, and sex, with no decline among white women of 80 years of age and older to a 55% decline among black men 40–49 years of age. Remarkably, black men experienced the largest drop within every 10-year age group. The authors noted that progress could be accelerated by applying cancer control knowledge across all segments of the population [8].

While the severity of cancers is often measured in number of deaths, the number of years of life lost (YLL) may be a more appropriate indicator of impact

on society [9]. These authors calculated the YLL of adult cancers in Norway for 2012 and for the prior 15-year period. Their results showed that cancer deaths in Norway in 2012 represented 25.8% of all adult deaths (28.7% in men and 23.1% in women). Cancer deaths represented 35.2% of all YLL, with a 5.0% higher fraction in females than in males (32.8% in men and 37.8% in women) [9].

The etiology of cancer is generally thought to be the product of gene and environmental interactions. Environmental exposures are typically low and to mixtures of constituents that occur indoors and outdoors. Goodson *et al.* hypothesized that low-dose exposures to mixtures of chemicals in the environment may be combining to contribute to environmental carcinogenesis [10]. They reviewed 11 hallmark phenotypes of cancer, with multiple priority target sites for disruption in each area and prototypical chemical disruptors for all targets. Dose–response characterizations and evidence of low-dose effects and cross-hallmark effects for all targets and chemicals were considered. In total, 85 examples of chemicals were reviewed for their actions on key pathways and mechanisms related to carcinogenesis. Although 59% of the chemicals caused low-dose effects, only 15% (13/85) were found to show evidence of a dose–response threshold. No dose–response information was found for the remaining 26% (22/85). The authors speculated that the cumulative effects of individual noncarcinogenic chemicals acting on different pathways in related systems, organs, tissues, and cells could synergize to produce carcinogenic outcomes. They concluded that additional research on carcinogenesis focused on low-dose effects of chemical mixtures needs to be rigorously pursued before the merits of their hypothesis can be further tested [10].

In a published poster abstract, Parkin and Paul [11] estimated the percentage of cancer in the United Kingdom in 2010 resulting from exposure to 14 major life style, dietary, and environmental risk factors. Prevalence and relative risks of exposure to factors, including tobacco smoking, consumption of four different dietary components (fruit and vegetables, meat, fiber, salt) alcohol use, occupation, infections, radiation, hormone use, overweight, physical exercise, and reproductive factors were used to estimate the number of cancers occurring in 2010 attributable to suboptimal exposure levels in the past. These 14 exposures were responsible for 42% of cancer in the United Kingdom in 2010 (males 44%, females 40%). Tobacco smoking was the most important, accounting for about 60,000 new cancers (18.5% of all cancer; 22% in men, 15% in women), with less than 2% being the result of exposure to environmental tobacco smoke. The four dietary components account for 9.4% of cancer (10.7% in men, 7.1% in women). In men, alcohol use (5.1%) and occupational exposures (4.7%) are next in importance and in women, overweight and obesity are next (nearly 7% of cancers). The study is cited because estimates of this kind provide a quantitative assessment of the impact of various exposures. However, they are not synonymous with the fraction of cancers that might reasonably be prevented by modification of exposures. As discussed by the authors, “this requires scenario