

Contents

Part I General Overview of Mitochondrial Genetics and Functions

1 Basic Mitochondrial Genetics, Bioenergetics, and Biogenesis	3
1.1 Introduction	3
1.2 The Mitochondrion	4
1.3 Contrasting Features of Mitochondrial and Nuclear Genetics	5
1.4 Mitochondrial Genomic Structure and Organization	13
1.5 Mitochondrial Microsatellites and D310	14
1.6 Mitochondrial Pseudogenes	15
1.7 The Respiratory Chain	16
1.7.1 The Electron Transport Chain	16
1.7.2 Coupling of the Proton Gradient with Oxidative Phosphorylation	21
1.7.3 The Respiratory Chain and Reactive Oxygen Species Production	21
1.8 Mitochondrial Biogenesis	22
1.8.1 Mitochondrial Genome Replication	22
1.8.2 Mitochondrial Genome Transcription	24
1.9 Control of Mitochondrial Biogenesis	28
1.9.1 Hormonal Control	28
1.9.2 Nuclear Respiratory Factors	29
1.9.3 Peroxisomal Proliferator Activator Receptor Gamma Co-Activator-1 α	30
1.9.4 Regulation of PGC-1	30
1.9.5 PGC-1 α -Related Coactivator	32
1.9.6 Myc Oncogene and Mitochondrial Biogenesis	32
1.10 Import of Nuclear-Encoded Proteins into Mitochondria	32
1.11 Mitochondrial Import of Cytosolic Transfer RNA	33
1.12 Conclusion	33
References	34

2	The Warburg Phenomenon and Other Metabolic Alterations of Cancer Cells	39
2.1	Introduction	39
2.2	Bioenergetics of Normal Cells	40
2.3	The Crabtree Effect	40
2.4	The Warburg Phenomenon	42
2.5	Molecular Basis of the Warburg Phenomenon	46
2.5.1	HK and Glycolysis	48
2.5.2	The PI3K/AKT Signaling Pathway and Glycolysis	49
2.5.3	The MYC Oncogene and Glycolysis	50
2.5.4	Hypoxia-Inducible Factor Pathway and Glycolysis	51
2.5.5	P53 and Glycolysis	55
2.6	Glutamine Metabolism in Cancer Cells	56
2.7	Lipid Metabolism in Cancer Cells	57
2.8	Citrate Metabolism by Prostate Glandular Epithelial Cells	58
2.9	Clinical Implications of Altered PCa Metabolism	59
2.9.1	Diagnostic Imaging of PCa	60
2.9.2	Screening for PCa Using Biofluids	61
2.9.3	PCa Prevention and Treatment	61
2.10	Conclusion	62
	References	62
3	Mitochondrial Control of Apoptosis and Cancer	67
3.1	Introduction	67
3.2	Cell Death Processes: The Conundrum of Semantics	68
3.3	Physiologic Importance of Apoptosis	69
3.4	Caspase Cascade	69
3.5	The Intrinsic or Mitochondrial Apoptotic Pathway	70
3.5.1	Mitochondrial Membrane Permeabilization	70
3.5.2	BCL-2 Family Members and Regulation of Mitochondrial Membrane Permeabilization	72
3.5.3	The Execution of Mitochondrial Apoptosis	75
3.5.4	Viral Control of Mitochondrial Apoptosis	76
3.5.5	Regulation of Intrinsic Apoptosis by Signaling Pathways	77
3.5.6	Mitochondrial Fission and Apoptosis	80
3.6	The Extrinsic Apoptotic Pathway	80
3.7	Evasion of Apoptosis by Cancer Cells	81
3.7.1	Cancer as a Defect in Apoptosis	82
3.7.2	Intrinsic Apoptotic Pathway Alterations in Cancer	82
3.7.3	Extrinsic Apoptotic Pathway Alterations in Cancer	84
3.8	Mitochondrial Genetic Defects and Apoptosis	85
3.9	Conclusion	87
	References	87

4 Mitochondrial-to-Nuclear Communications in Cancer	93
4.1 Introduction	93
4.2 <i>Succinate Dehydrogenase and Fumarate Hydratase</i>	
Mutations and Cancer	94
4.2.1 <i>SDH</i> Mutations and Cancer	95
4.2.2 Genetics and Clinical Features of <i>Fumarate Hydratase</i>	
Mutations	100
4.2.3 Genetic Testing and Counseling for <i>SDH</i> and	
<i>FH</i> Mutations	102
4.2.4 Mechanism of Tumor Induction by <i>SDH</i> and <i>Fumarate</i>	
<i>Hydratase</i> Mutations	105
4.3 Mitochondria-to-Nuclear Stress Signaling in Cancer	108
4.4 Nuclear Integration of Mitochondrial Genome Fragments	
and Possible Oncogene Induction	110
4.5 Conclusion	111
References	112

Part II Mitochondrial Genetic Alterations in Cancer

5 Types of Mitochondrial Genetic Alterations in Cancer	119
5.1 Introduction	119
5.2 Mitochondrial Haplotypes and Haplogroups	120
5.3 Mitochondrial DNA Polymorphisms and Somatic Mutations	121
5.4 Mitochondrial Microsatellites	123
5.4.1 Discovery of D310 Instability as a Mutational	
Hot-Spot in Cancer	123
5.4.2 Mechanism of mtMSI	124
5.4.3 Clinical Utility of mtMSI	124
5.5 Mitochondrial Genome Rearrangements	125
5.6 Mitochondrial DNA Copy Number (Content) Changes	127
5.7 Novel Mitochondrial Transcripts in Cancer	127
5.8 Pitfalls Associated with Scoring Mitochondrial	
DNA Mutations	129
5.9 Criticisms of Somatic Mitochondrial DNA	
Mutations in Cancer	130
5.10 Natural Selection Explains Mitochondrial DNA Mutations	
in Cancer	131
5.11 Conclusion	131
References	132
6 Mitochondrial Genetic Alterations in Cancer I: Skin, Head and	
 Neck, Salivary Glands, Thyroid, Breast, Lung, Esophageal, Gastric,	
 Colorectal, Pancreatic, Liver and Gallbladder Cancers	135
6.1 Introduction	135

6.2	Skin Cancer	136
6.2.1	Melanoma	137
6.2.2	Nonmelanoma Skin Cancer	139
6.3	Head and Neck Cancer	139
6.4	Salivary Gland Cancer	142
6.5	Thyroid Cancer and Parathyroid Adenoma	142
6.6	Breast Cancer	145
6.7	Lung Cancer	149
6.8	Esophageal Cancer	150
6.9	Gastric Cancer	151
6.10	Colorectal Cancer	153
6.11	Pancreatic Cancer	156
6.12	Hepatocellular Carcinoma	157
6.13	Gallbladder Cancer	159
6.14	Conclusion	159
	References	159
7	Mitochondrial Genetic Alterations in Cancer II: Renal, Urinary Bladder, Prostate, Ovarian, Endometrial, Cervical, Nervous System, Hematologic, and Connective Tissue Cancers	167
7.1	Introduction	167
7.2	Renal Cancer	167
7.3	Bladder Cancer	170
7.4	Prostate Cancer	170
7.5	Ovarian Cancer	173
7.6	Endometrial Cancer	175
7.7	Cervical Cancer	176
7.8	Nervous System Tumors	177
7.9	Hematologic Malignancy	178
7.10	Connective Tissue Cancer	181
7.11	Conclusion	182
	References	182
8	Mitochondrial Genome Rearrangements and Copy Number Changes in Cancer	187
8.1	Introduction	187
8.2	Overview of mtDNA Deletion Disorders	188
8.3	Mitochondrial Genome Deletions in Cancer	188
8.4	Is the CD a Tumor Suppressor?	198
8.5	mtDNA Content Alterations in Cancer	198
8.5.1	Cancers with Increased mtDNA Content	199
8.5.2	Cancers with Reduced mtDNA Content	202
8.6	Possible Reasons for mtDNA Repletion or Depletion in Cancer	203

8.6.1 Increased mtDNA Copy Number	203
8.6.2 Decreased mtDNA Copy Number	204
8.7 Postulated Mechanisms of Deletion Formation	204
8.8 Control of mtDNA Deletions	206
8.9 Conclusion	207
References	207
9 Functional Importance of Mitochondrial Genetic Alterations in Cancer	213
9.1 Introduction	213
9.2 Mitochondrial DNA Mutations in Cancer: Cause or Consequence?	214
9.3 Functional Consequences of Mitochondrial DNA Mutations on Mitochondrial Biogenesis in Cancer	215
9.4 Techniques Employed to Study the Contribution of Mitochondrial DNA Mutations in Cancer	217
9.4.1 Generating p0 Cells	218
9.4.2 Producing Transmitochondrial Hybrids (Cybrids)	219
9.4.3 Nuclear Transfection of Mutant Mitochondrial DNA	220
9.5 Contribution of Mitochondrial DNA Changes to Cancer Biology	221
9.5.1 Cancer Risk Predisposition	221
9.5.2 Cancer Initiation	222
9.5.3 Cancer Cell Proliferation and Growth	224
9.5.4 Cancer Progression and Metastasis	226
9.5.5 Acquisition of Hormonal Independence and Chemoresistance by Cancer Cells	227
9.5.6 Contribution of Mitochondrial Genome Changes to the Development of Oncocytic Tumors	228
9.6 Mitochondrial Membrane Potential and Cancer	230
9.7 Collaborative Evidences from Clinical Studies	231
9.8 Conclusion	232
References	233
10 The Role of Mitochondrial Reactive Oxygen Species in Cancer	237
10.1 Introduction	237
10.2 ROS Production by Mitochondria	238
10.3 Biomolecular Targets of ROS	241
10.4 Modulation of Intrinsic Apoptosis by ROS	242
10.5 ROS and Hypoxia-Inducible Factor Stabilization in Cancer	243
10.6 ROS and p53 Functions	244
10.7 ROS and Oncogenic Signaling Pathways	244
10.7.1 MAPK Pathway	245

10.7.2	PI3K/AKT Pathway	246
10.7.3	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells Pathway	246
10.7.4	Activator Protein 1	247
10.7.5	Protein Kinase C	247
10.7.6	Myc Oncogene	248
10.8	ROS and Carcinogenesis	248
10.9	Ameliorating the Harmful Effects of ROS	250
10.10	Conclusion	252
	References	252

Part III Clinical Applications of Mitochondrial Genome Changes in Cancer

11	Mitochondrial DNA Measurement in Exfoliated Cells for Cancer Detection and Monitoring: The Copy Number Advantage	259
11.1	Introduction	259
11.2	Tumor Signatures in Biofluids	260
11.3	Mitochondrial Genome Changes in Biofluids of Cancer Patients	262
11.3.1	Blood (Serum and Plasma)	262
11.3.2	Salivary Rinses	265
11.3.3	BAL and Sputum	266
11.3.4	Nipple Aspirate Fluid and Ductal Lavage	266
11.3.5	Urine	267
11.3.6	Cerebrospinal Fluid	268
11.3.7	Other Biofluids	268
11.3.8	Exfoliated Skin Cells for Skin Cancer Detection	269
11.4	Clinical Utility of Mitochondrial DNA Changes in Biofluids	269
11.5	Conclusion	271
	References	271
12	Early Cancer Detection and Monitoring Using Changes in the Mitochondrial Genome as Biosensors	275
12.1	Introduction	275
12.2	Field Cancerization Demonstrated by Mitochondrial Genome Changes	278
12.3	Field Cancerization Is a General Carcinogenic Phenomenon: Evidence from Nuclear Genetic Markers	281
12.4	Clinical Importance of Cancer Field Molecular Signatures	288
12.4.1	Appropriateness of Control Tissue in Cancer Studies	289

12.4.2 Risk Assessment, Early Cancer Detection, Chemoprevention, and Disease Monitoring	289
12.4.3 Tumor Margins and Recurrences	291
12.5 Conclusion	291
References	292
13 Analysis of Mitochondrial Genome Alterations in Cancer	297
13.1 Introduction	297
13.2 Preparation of Clinical Samples for Mitochondrial Genome Analysis in Cancer	298
13.3 Analysis of Mitochondrial Genome Point Mutations in Cancer	299
13.3.1 Diagnostic Approaches	299
13.4 Analysis of Mitochondrial Genome Deletions and Content Changes	309
13.4.1 Southern Blotting	310
13.4.2 Quantitative Polymerase Chase Reaction	310
13.5 Quality Assurance Issues in Mitochondrial DNA Analysis	317
13.6 Conclusion	318
References	318
14 “Mitocans”: Agents Targeting Mitochondria to Kill Cancer Cells	321
14.1 Introduction	321
14.2 Chemotherapy Targets	322
14.2.1 The Intrinsic Apoptotic Pathway	322
14.2.2 Targeting Glycolysis to Kill Cancer Cells	332
14.2.3 Targets of Redox Homeostasis	335
14.2.4 Targeting Membrane Potential Changes	336
14.2.5 Cancer Mitochondrial DNA Depletion as a Strategy	336
14.2.6 Delivery of Toxic Compounds to Mitochondria Using Differential Receptor Expression by Cancer Cells	337
14.3 Conclusion	338
References	338
Index	345