
Contents

Coupling Between Transcription and Alternative Splicing	1
1 Introduction	2
2 Alternative Splicing and Its Regulation	3
3 Splicing Co-Transcriptionality and Coupling.	5
4 Molecular Mechanisms of Coupling.	7
5 Evidence of Functional Coupling Between Transcription and Alternative Splicing.	9
6 Consequence of Co-Transcriptionality in Splicing	10
7 Models for Co-Transcriptional Regulation of Alternative Splicing.	12
7.1 The Recruitment Model	12
7.2 The Kinetic Model	14
8 Concluding Remarks	19
References	20
 Detection of Alternatively Spliced or Processed RNAs in Cancer Using Oligonucleotide Microarray	25
1 Introduction	26
2 Detection of Alternatively Spliced RNA.	26
2.1 Exon-Junction Microarray.	26
2.2 Ligation-PCR Followed by Microarray Detection	27
2.3 Exon Microarray	28
3 Detection of Alternatively Processed RNA Using Genomic Tiling Microarray	30
3.1 The Design of Genomic Tiling Microarray.	30
3.2 Tiling Microarray Used in the Transcriptome Mapping and the ENCODE Project.	31
3.3 Detection of Unspliced or Partially Spliced RNA by Tiling Microarray	32
3.4 Detection of Alternatively Processed RNAs in Breast Cancer Using Tiling Array	33
4 Transcriptome Analysis by Direct Sequencing	35
5 Summary and Conclusion.	36
References	36

Cancer-Associated Perturbations in Alternative Pre-messenger

RNA Splicing	41
1 Introduction	43
2 Function of Cancer-Associated Splice Variants	44
2.1 Cellular Proliferation	46
2.2 Cellular Invasion	46
2.3 Angiogenesis.	59
2.4 Resistance to Apoptosis	59
2.5 Multidrug Resistance	60
3 Alternative Splicing Control: Basic Principles.	60
4 Molecular Basis for Splicing Alterations in Cancer	62
4.1 Mutations at Splice Sites and in Auxiliary Elements	63
4.2 Alterations in the Activity of Splicing Proteins	64
5 Outlooks and Challenges	73
5.1 Global Detection of Splicing Variation in Cancer	73
5.2 Depleting Specific Splice Isoforms	75
5.3 Reprogramming Alternative Splicing	76
6 Conclusions	78
References	78

Alternative Splicing of Tumor Suppressors and Oncogenes.

1 Introduction	96
1.1 Sequence Elements and Protein Factors Controlling Alternative Splicing	98
2 Alternative Splicing and Cancer	100
2.1 Alternative Splicing and Apoptosis	102
2.2 Alternative Splicing and Cell Membrane Proteins	103
2.3 Alternative Splicing and Cell Invasiveness	105
2.4 Alternative Splicing and Signal Transduction	109
3 Concluding Remarks	111
References	112

MicroRNAs in Cancer.

1 Introduction	120
2 Biogenesis of miRNAs.	120
3 The Dysregulation of miRNAs in Cancer.	122
4 miRNAs and Cancer Metastasis	123
5 miRNAs, Key Modulators in Cell Signaling Pathways.	125
5.1 PTEN/PI3K/AKT Signaling Pathway	125
5.2 MAPK/ERK Signaling Pathway	127
5.3 NF- κ B Signaling Pathway	128
5.4 TGF- β and mTOR Pathways.	128

6	Therapeutic Potential for miRNAs.	128
7	Concluding Remarks	129
	References	129

The Perinucleolar Compartment: RNA Metabolism and Cancer 139

1	Introduction	140
1.1	Structure of the PNC	140
1.2	Molecular Components of the PNC	140
2	The PNC and RNA Metabolism	142
2.1	The PNC is Likely Involved in RNA Processing.	142
2.2	PNC is Enriched with Pol III Transcripts, but not Pol I or Pol II RNAs	143
2.3	Novel RNP Associates with the PNC.	143
2.4	Potential Functions of the PNC	144
3	The PNC and Malignant Transformation	146
3.1	PNC Selectively Forms in Metastatic Solid Tumor Cells	146
3.2	The PNC and Metastatic Behavior.	146
3.3	PNC is not a Marker of Differentiation or Growth Rate	147
3.4	Why does the PNC Form in Transformed Cells?	148
4	Potential Utilization of the PNC	149
4.1	Prognostic Marker for Solid Tumors	149
4.2	Anti-Cancer Drug Discovery Marker	150
	References	150

Regulation of ARE-mRNA Stability by Cellular Signaling:

Implications for Human Cancer. 153

1	Introduction	154
2	AU-Rich Elements.	155
3	ARE-Binding Proteins	155
3.1	TTP, BRF-1, and BRF-2	156
3.2	KSRP.	157
3.3	AUF1/hnRNP D	158
3.4	HuR.	159
3.5	TIA-1 and TIAR	160
3.6	Other ARE-Binding Proteins.	161
4	Signal Transduction Pathways Regulating ARE-mRNA Decay	162
4.1	MAPK Pathways.	162
4.2	PI3K/Akt-PKB	165
5	Perspective: Implications for Cancer	165
	References	167

Alternative Pre-mRNA Splicing, Cell Death, and Cancer	181
1 Introduction	182
2 Pre-mRNA Splicing and Alternative Splicing Regulation	183
3 Alternative Splicing Regulation of Cell Death Genes	184
3.1 Alternative Splicing Isoforms of Genes Encoding Caspases and Other PCD-Related Proteases	184
3.2 Bcl-2 Superfamily	185
3.3 Death Ligands and Death Receptors	186
3.4 Intrinsic Cell Death Signals	188
3.5 Inhibitor of Apoptosis Proteins (IAPs)	189
3.6 Cell Death-Related DNases and Their Regulators	190
3.7 Mitochondrial Cell Death Proteins	190
3.8 Autophagy, Cell Death, and Alternative Splicing of Autophagy Regulatory Genes	191
4 Alternative Splicing: A Versatile Mechanism for Regulating Expression and Function of Cell Death Genes	192
4.1 Regulation of Subcellular Localization	193
4.2 Modulating Functional Activities	193
4.3 Altering mRNA Stability or Translational Efficiency	194
5 Molecular Mechanisms Regulating Alternative Splicing of Cell Death Genes	194
5.1 Splicing Signals, Splicing Machinery, and Alternative Splicing Regulators	194
5.2 Mechanisms Underlying Alternative Splicing Regulation of PCD Genes	195
5.3 Complex Networks Linking Alternative Splicing, Cell Death, and Other Processes	197
6 Cell Death Regulation, Pre-mRNA Splicing, and Cancer	198
6.1 Splicing Factors, Splicing Variants, and Cancer	198
6.2 Death Receptors and Cancer	198
6.3 BCL-2 Family and Cancer	199
6.4 Caspase Alternative Splicing and Cell Death Regulation in Cancer	199
6.5 IAPs and Cancer	200
6.6 Cell Death-Related DNases and Their Regulators	200
6.7 Mitochondrial Cell Death Proteins and Cancer	201
6.8 Defective Autophagy and Cancer	201
7 Concluding Remarks	201
References	202
 Oligonucleotide Therapeutics in Cancer	 213
1 Introduction	214
2 Splice Switching Oligonucleotides	214
3 Oligonucleotide Chemistry	215

3.1	RNAse H-Competent Chemistries (First Generation)	215
3.2	RNAse H Non-Competent Chemistries (Second Generation)	216
4	Positive Readout Assay for Antisense Oligonucleotide Activity	218
5	Splice Switching Oligonucleotide Targets in Cancer	218
5.1	Bcl-x (BCL2L1)	218
5.2	HER2.	220
5.3	FGFR1	221
5.4	ATM	221
5.5	PSMA	222
6	Other Applications of SSO Technology	222
6.1	ESSENCE	222
6.2	TOSS.	223
7	RNA Interference	223
8	Inhibition of Translation Initiation and Other Antisense Approaches.	224
9	Antisense-Based Therapeutics in Cancer Clinical Trials.	224
9.1	First Generation: Phosphorothioate DNA Oligonucleotides	225
9.2	Second Generation: Phosphorothioate Gapmers.	225
	References	227

Clinical Perspective on Chemo-Resistance and the Role

of RNA Processing	235
1 Introduction	236
2 Alternative Splicing and Drug Delivery	237
2.1 Alternatively Spliced Steroid Receptors	237
2.2 Multidrug Resistance	238
3 Alternative Splicing and Drug Metabolism and Activation	239
4 Alterations in the Mechanisms of Drug Action	240
5 Mechanisms of Alternative Splicing Associated with Resistance to Cancer Therapies.	241
6 Summary and Conclusions	243
References	243



<http://www.springer.com/978-3-642-31658-6>

RNA and Cancer

Wu, J.Y. (Ed.)

2013, XIII, 245 p., Hardcover

ISBN: 978-3-642-31658-6