

Contents

Preface XI

List of Contributors XIII

1	Microarrays in Systems Neurobiology and Translational Neuroscience – From Genome Research to Clinical Applications	1
	<i>Jeremy A. Miller and Daniel H. Geschwind</i>	
1.1	Introduction	1
1.2	Gene Expression Before Microarrays	2
1.2.1	High-Throughput Gene Expression Techniques	2
1.2.2	Contemporaneous Alternatives to Microarrays	3
1.2.3	Microarray Technologies	4
1.2.3.1	One-Color Oligonucleotide Arrays	4
1.2.3.2	Two-Color Arrays	5
1.2.3.3	Bead-Based Arrays	5
1.3	Designing and Implementing a Microarray Experiment – From Start to Finish	5
1.3.1	Choosing the Proper Microarray Platform	6
1.3.2	Preparing the Tissue for Hybridization	6
1.3.3	Single-Cell Assays and Tissue Heterogeneity	7
1.3.4	Microarray Hybridization and Scanning	8
1.3.5	Preprocessing	8
1.3.6	Gene Expression Analyses	9
1.3.7	Analytical Challenges	9
1.3.8	Validating Results	13
1.4	Clinical Applications	13
1.4.1	Neurological Disease-Relevant Research	13
1.4.1.1	Incipient Alzheimer's Disease	15
1.4.1.2	Using Animal Models to Study Neurodegeneration	16
1.4.1.3	Determining Gene Pathways Using Meta-Analysis	16
1.4.2	Cancer Research	17
1.4.2.1	Tumor Classification and Patient Diagnosis	17

1.4.2.2	Determining Patient Prognosis	18
1.4.2.3	Predicting Therapeutic Response to Treatment	18
1.4.2.4	Determining Therapeutic Targets for Cancer	19
1.4.3	Using Peripheral Tissues as a Substitute for Brain Tissue	20
1.4.3.1	Gene Expression Profiling of Disease	20
1.4.3.2	Dividing Complex Phenotypes into Subtypes Using Microarrays	21
1.4.3.3	Applying Blood Classification to Treatments	22
1.4.3.4	Advantages and Disadvantages of Using Blood Genomics for Brain Disorders	23
1.4.3.5	Pure Cell Line Assays in Peripheral Blood	23
1.4.4	Other Types of Microarrays in Clinical Setting	24
1.4.4.1	Gene Dose, Molecular Karyotyping, and Chromosomal Abnormalities	24
1.4.4.2	SNP Genotyping and Beyond	24
1.4.5	Future Clinical Applications: Pharmacogenomics	25
	References	26
2	A Meta-Analysis of Large-Scale Gene Expression Studies of the Injured PNS: Toward the Genetic Networks That Govern Successful Regeneration	35
	<i>Floor J. Stam, Matthew R. J. Mason, August B. Smit, and Joost Verhaagen</i>	
2.1	Introduction	35
2.2	Lesion Models in the Peripheral Nervous System	35
2.2.1	Sciatic Nerve	36
2.2.2	Facial Nerve	36
2.2.3	Postganglionic Trunk of the Superior Cervical Ganglion	37
2.2.4	Injury Types	37
2.3	Cellular Events After Injury	37
2.3.1	Regeneration After Dorsal Root Lesion is Limited Due to a Weak Neuronal Response to Axotomy	38
2.3.2	Injury Signals	38
2.3.3	Regeneration-Associated Gene Expression	39
2.4	Large-Scale Screening Efforts to Find Novel Regeneration-Associated Genes	40
2.4.1	Global Gene Expression Changes After Neuronal Injury Found by Gene Expression Profiling Studies	40
2.4.2	Biological Processes Affected by Peripheral Nerve Injury	45
2.4.3	Identification of Novel Regeneration-Associated Genes by Microarray Analysis	46
2.5	Developing New Insights into the Molecular Biology of Regenerative Neurite Outgrowth: From Single Gene to Genetic Networks	47
2.5.1	Strategies to Enhance the Revenue of Profiling Regenerating Neurons	47

- 2.5.2 Open Screening for Regeneration-Associated Changes in the Transcriptome and (Phospho)Proteome 49
- 2.5.3 High-Throughput Screening for the Function of Target Genes 50
- 2.5.4 Finding Target Genes of Regeneration-Associated Transcription Factors 50
- 2.5.5 *In Silico* Approaches to Transcriptional Regulatory Network Elucidation 51
- 2.5.6 From Transcriptional Regulatory Network to Regeneration 51
- References 52

3 Analyzing Complex Gene Expression Profiles in Sensorimotor Cortex Following Spinal Cord Injury and Regeneration Promoting Treatment 61

Fabian Kruse, Nicole Brazda, Patrick Küry, Frank Bosse, and Hans W. Müller

- 3.1 Introduction 61
- 3.2 Scar-Suppressing Treatment of SCI 62
- 3.3 Experimental Design 63
 - 3.3.1 Treatment Paradigms and Animal Groups 63
 - 3.3.2 Corticospinal Tract Transection 64
 - 3.3.3 Cortical Tissue Preparation and Total RNA Isolation 64
 - 3.3.4 Probe Labeling and Array Hybridization 65
- 3.4 Data Analysis 65
 - 3.4.1 Affymetrix GeneChip Technology 65
 - 3.4.2 Variations 66
 - 3.4.3 Impact of the Experimental Setup 66
 - 3.4.4 Low-Level Analyses 67
 - 3.4.4.1 Microarray Suite (MAS) 67
 - 3.4.4.2 Model-Based Expression Indexes (MBEI) 68
 - 3.4.4.3 Robust Multiarray Average 69
 - 3.4.4.4 GC-RMA 71
 - 3.4.4.5 Probe Logarithmic Intensity Error (PLIER) 72
 - 3.4.5 Combination of Preprocessing Methods 72
 - 3.4.6 Statistical Analysis 73
 - 3.4.7 From Raw Data to Biological Meaning 75
 - 3.4.7.1 Chip Chat 75
 - 3.4.7.2 Implemented Thresholds 76
 - 3.4.8 Biological Pathways and Ontology Information 76
- 3.5 Results and Discussion 78
 - 3.5.1 Expression Patterns 78
 - 3.5.2 Summary 83
 - References 84

- 4 Unraveling Plasticity of Dorsal Root Ganglion and Spinal Cord Neurons Using cDNA Arrays 91**
Xu Zhang, Hua-Sheng Xiao, and Lan Bao
- 4.1 Identification of Regulated Molecules in DRG After Peripheral Nerve Injury 92
- 4.1.1 Neuropeptides and Neuropeptide Receptors 92
- 4.1.2 Molecules Related to Synaptic Transmission 93
- 4.1.3 Neurotransmitter Receptors and Ion Channels 95
- 4.1.4 Molecules for Survival or Regulating Gene Expression 96
- 4.2 Modification of Gene Expression in the Dorsal Horn of Spinal Cord 97
- 4.2.1 Ion Channels 97
- 4.2.2 Neurotransmitter/Neuromodulator Receptors 97
- 4.2.3 Signal Transduction Molecules 99
- 4.3 Potential Pharmacological Impact of the Regulated Molecules 99
- 4.4 Future Application of Gene Array 100
- References 101
- 5 The Role of Gene Expression Dependent Molecular Pathways in Axon Plasticity and Neuron Repair Following Acute CNS Injury 105**
Simone Di Giovanni
- 5.1 Introduction 105
- 5.2 The Mechanisms that Determine Functional Recovery Following Acute CNS Damage 108
- 5.3 Repair and Tissue Plasticity Gene Expression Changes Following Acute CNS Injury 111
- 5.4 Gene Expression Profiles and Gene Clusters Related to Axon Sprouting and Regeneration 113
- 5.5 The Role of Transcription Factors in the Control of Axon Growth and Regeneration 117
- 5.6 Therapeutic Implications for Neurodegenerative Disorders 119
- 5.7 Future Perspectives 122
- References 124
- 6 Axonal mRNA in Regeneration 135**
Christina F. Vogelaar and James W. Fawcett
- 6.1 Introduction 135
- 6.2 A Link Between Axon Regeneration and Local Protein Synthesis 136
- 6.3 Axonal mRNA Update 136
- 6.4 Axonal RNA Transport and Translation in Axon Guidance 141
- 6.4.1 Growth Cone Guidance of *Xenopus* Retinal Axons is Dependent on Axonal Protein Synthesis 141
- 6.4.2 Growth Cone Guidance is Mediated by Asymmetrical Transport and Translation of Selective mRNA Molecules 141

6.5	Axonal RNA in Mammalian Axons	144
6.5.1	Axon Guidance in Rat Dorsal Root Ganglion Axons	144
6.5.2	RNA Binding Proteins: A Link Between Axonal RNA and Axon Maintenance	144
6.5.3	Conditioning Lesioned Adult Rat DRG Axons	145
6.6	Summary and Conclusions	146
	References	147
7	Proteomic Approaches to Axon Injury – Postgenomic Approaches to a Posttranscriptional Process	153
	<i>Izhak Michaelevski and Mike Fainzilber</i>	
7.1	Rapid Responses to Injury	153
7.2	Retrograde Injury Signaling via Molecular Motors	154
7.3	Posttranscriptional Mechanisms in Axon Maintenance or Regrowth After Injury	156
7.4	Proteomics in Studies of Axon Injury Responses	157
7.5	Proteomics of Retrograde Injury Signals – From Local Translation to Signal Identification	158
7.6	Differential Proteomics in Central versus Peripheral Axon Tracts	159
7.7	Proteomics in Regenerating or Degenerating Axons	160
7.8	Moving Forward – Technical Developments with Potential Application in Neuroproteomics	161
7.9	Conclusions	162
	References	163
8	Genomics Approaches to the Study of Neurodegeneration	167
	<i>Jeanine Jochems, Peter Buckley, and James Eberwine</i>	
8.1	Introduction	167
8.2	Causes of Neurodegeneration	168
8.2.1	Alzheimer's Disease	168
8.2.2	Huntington's Disease	168
8.2.3	Parkinson's Disease	169
8.2.4	Amyotrophic Lateral Sclerosis	169
8.2.5	Common Processes Leading to Pathological Protein Aggregation in Neurodegenerative Diseases	170
8.2.6	Aging	170
8.3	Gene Expression Studies in Traumatic Brain and Spinal Cord Injury	172
8.3.1	Methodological Considerations	172
8.3.2	Spinal Cord	174
8.3.3	Traumatic Brain Injury	175
8.4	Concluding Remarks	177
	References	177

9	Redox Proteomics and Metabolic Proteins in Brain of Subjects with Alzheimer's Disease, Mild Cognitive Impairment, and Models Thereof	181
	<i>Rukhsana Sultana, Tanea Reed, and D. Allan Butterfield</i>	
9.1	Oxidative Stress	181
9.2	Redox Proteomics	182
9.2.1	Two-Dimensional Electrophoresis (2-DE)	184
9.2.2	Mass Spectrometry and Database Searching	185
9.3	Oxidative Damage in AD	186
9.4	Role of Identified Energy-Related Proteins in AD Brain	188
9.5	Oxidative Stress in MCI	190
9.6	Models of Alzheimer's Disease	190
9.6.1	Cell Culture Model	191
9.6.2	SAMP8	192
9.6.3	Synaptosomal Model	192
9.6.4	Intracerebral Ventricular Model	193
9.6.5	<i>Caenorhabditis elegans</i> Model	194
9.7	Conclusions	194
	References	195
10	Gene Expression Profiling of Gliomas – Improving the Understanding of Glioma Biology and Paving the Way for Molecular Classification	209
	<i>Markus J. Riemenschneider and Guido Reifenberger</i>	
10.1	Introduction	209
10.2	Expression Profiling and Glioma Classification	211
10.3	Progression-Associated Gene Expression Changes in Gliomas	215
10.4	Expression Signatures Relating to Tumor Location	217
10.5	Pathway-Associated Expression Signatures and Targeted Therapies	218
10.6	Expression Profiling of Selected Tumor Cell Subpopulations – Deciphering Tumor Heterogeneity	219
10.7	Summary and Outlook	223
	References	224
	Index	229