

Contents

Contributors	v
Preface	xi

CHAPTER 1 Overview of Genetic Models of Autism Spectrum Disorders

Jheel Patel, Jodi L. Lukkes, Anantha Shekhar	1
1. Introduction	2
2. Theories of ASD Development	6
2.1. Neuronal Number and Growth	6
2.2. Dendritic Morphogenesis	7
2.3. Excitation-Inhibition Imbalance	9
2.4. Neuroinflammation	9
2.5. Environmental Factors	10
3. Mechanisms of ASD Development	12
3.1. Disruptions in Synaptic Transmission	12
3.2. Disruptions in Intracellular Kinase Signaling Pathways	16
4. Limitations and Challenges of Genetic Animal Models	19
5. Future of Genetic Models	22
5.1. Genome Editing	22
5.2. Modulation of Neuronal Activity	23
5.3. Biological Network Studies	24
5.4. Stem Cell Approaches	24
5.5. Gut Microbiome Connection	24
6. Conclusions	25
Acknowledgments	26
References	26

CHAPTER 2 Neurofibromatosis Type 1 as a Model System to Study Molecular Mechanisms of Autism Spectrum Disorder Symptoms

Andrei I. Molosh, Anantha Shekhar	37
1. Introduction	38
2. Background	38
3. Cognitive and Behavioral Problems in Patients With NF1	39
4. NF1 Genetically Engineered Mouse as Model Systems	40
5. The Role of Neurofibromin in Modulation of Ras/ERK, PI3K/mTOR and cAMP Intracellular Pathways	42

6. Amelioration of Cognitive Problems in Mice and Humans	
Using Different Pharmacological Tools.....	46
6.1. MEK Inhibitors.....	46
6.2. Pak1 Inhibitors.....	47
6.3. Statins.....	49
6.4. GABA Inhibitors.....	50
6.5. Other Therapeutic Candidates.....	51
7. Concluding Remarks and Perspectives.....	52
Acknowledgment.....	53
References.....	53

CHAPTER 3 ERK/MAPK Signaling and Autism Spectrum Disorders..... 63

Joseph Vithayathil, Joanna Pucilowska, Gary E. Landreth

1. Introduction.....	63
2. ERK/MAPK Pathway and Autism.....	64
3. Discovery of MAPK/ERK Signaling.....	66
4. MAPK Pathway Activation.....	68
5. ERK/MAPK Pathway Regulation.....	70
6. Developmental Roles for ERK Signaling.....	73
7. ERK/MAPK Signaling and Synaptic Plasticity.....	75
7.1. ERK Signaling at the Synapse.....	79
7.2. Local Translation.....	79
7.3. ERK Signaling in the Nucleus.....	80
8. The Role of ERK/MAPK Signaling in Behavior.....	81
8.1. Spatial Memory.....	81
8.2. Associative Learning.....	81
8.3. Reward/Addiction Behaviors.....	82
8.4. Social Behaviors.....	82
9. ERK Signaling in Rasopathies and ASD Models.....	83
9.1. Neurofibromatosis Type 1.....	83
9.2. Noonan Syndrome.....	84
9.3. Costello Syndrome.....	85
9.4. Cardio-Facio-Cutaneous Syndrome.....	86
10. Mutations of ERK-Pathway Related Signaling Proteins and ASD.....	86
10.1. SynGAP1.....	86
10.2. FMR1.....	87
10.3. 16p11.2 Deletion/Duplication.....	89
10.4. DiGeorge Syndrome (22q11 Deletion Syndrome).....	90

10.5. Rett Syndrome and Tuberous Sclerosis.....	90
10.6. BTBR Inbred Mouse Strain.....	91
11. Conclusion.....	91
References.....	92

CHAPTER 4 From Bedside to Bench and Back: Translating ASD Models..... 113

**Hayley P. Drozd, Sotirios F. Karathanasis, Andrei I. Molosh,
Jodi L. Lukkes, D. Wade Clapp, Anantha Shekhar**

1. Introduction.....	114
2. Optimizing Clinical Concepts of ASD—"The Bedside Efforts".....	115
2.1. Genetic Biomarkers.....	119
2.2. Imaging Biomarkers.....	120
2.3. Serum Biomarkers.....	121
2.4. Multimodal Analysis.....	122
3. Optimizing the Preclinical Model—"The Bench Efforts".....	124
4. Translating to Therapies—"Back to the Bedside".....	128
4.1. Bench-to-Bedside Pharmacotherapy.....	128
4.2. Bedside-to-Bedside Pharmacotherapy.....	134
4.3. Measuring Outcomes in Pharmacotherapy.....	136
5. Conclusions.....	137
Acknowledgments.....	137
References.....	137

CHAPTER 5 Studying Child Development in Genetic Models of ASD..... 159

Shruti Garg, Jonathan Green

1. Phenotype and Genotype in ASD.....	160
2. Monogenic Syndromic ASD and the Comparative Method.....	162
3. The ASD Behavioral Phenotype Across Genetic Models of ASD.....	163
3.1. Summary.....	167
4. Developmental Trajectory of ASD Across Genetic Syndromes.....	167
4.1. Structural and Functional Brain Abnormalities.....	168
4.2. Neurocognitive Markers.....	170
4.3. Motor Function.....	171
4.4. Behavior Development.....	172
4.5. Summary.....	172

5. Experimental Intervention	173
5.1. Fragile X Disorder (FXS): GABA-Glutamate Balance	174
5.2. NF1: The MAPK/ERK Cell Signaling Pathway	177
5.3. TSC: The mTOR Pathway	179
5.4. Rett and Phelan-McDermid Syndromes: Growth and Neurotrophic Factors	179
6. Summary	180
References	182

**CHAPTER 6 Measurement Considerations in Pediatric
Research on Autism Spectrum Disorders 193**
Karin S. Walsh, Srishti Rau

1. Introduction	193
2. Prevalence	194
2.1. In the General Population	194
2.2. In Genetic Syndromes	195
3. Diagnostic Guidelines	196
3.1. Level 1—Screening	196
3.2. Level 2: Comprehensive Evaluation	197
4. Assessing ASD Symptomatology	198
4.1. Parent Report	198
4.2. Diagnostic Observation	199
5. Intellectual and Adaptive Assessment	200
6. Language Assessment	202
7. Psychiatric Comorbidities	203
7.1. Sleep	203
7.2. Attention-Deficit/Hyperactivity Disorder	204
7.3. Anxiety	204
7.4. Obsessive Compulsive Disorder	205
7.5. Depression	205
7.6. Bipolar Disorder	206
7.7. Externalizing Disorders	206
8. NF1 as a Model for Examining ASD in Genetic Syndromes...	207
9. Conclusions	209
References	209