

Contents

Contributors.....	ix
Preface.....	xi

The Molecular Basis of Translational Control 1

Christopher S. Fraser

I. Introduction.....	2
II. Initiation Pathway Overview.....	3
III. Generating a Pool of 40S Ribosomal Subunits.....	6
IV. Preparing the 40S Subunit for Binding mRNA.....	8
V. eIF1 and eIF1A.....	8
VI. Initiator tRNA Recruitment to the 40S Subunit.....	10
VII. Regulating Ternary Complex Availability.....	13
VIII. The Role of eIF3 in 43S Complex Formation.....	14
IX. eIF5.....	17
X. Controlling mRNA Recruitment to the 40S Subunit.....	17
XI. Eukaryotic mRNA Characteristics.....	18
XII. Recruitment of mRNA to the 43S Complex.....	20
XIII. Ribosomal Scanning and Initiation Codon Recognition.....	25
XIV. Ribosomal Subunit Joining.....	28
XV. Regulating the Initiation Pathway.....	30
XVI. The Mechanism of Translation Elongation.....	30
XVII. Translation Termination.....	32
XVIII. Perspectives.....	34
References.....	35

Cell Signaling in Protein Synthesis: Ribosome Biogenesis and Translation Initiation and Elongation . . . 53

Sarah J. Mahoney, Jamie M. Dempsey, and John Blenis

I. Introduction.....	54
II. Translation: The Regulated Steps of Ribosome Biogenesis and Translation Initiation and Elongation.....	55
III. Signaling Pathways that Control Translation.....	64
IV. Signaling and Translation Initiation.....	72

V. Signaling and Elongation	81
VI. Signaling and Ribosome Biogenesis	84
References	92

Ribosomal Protein S6 Kinase: From TOP mRNAs to Cell Size 109

Oded Meyuhas and Avigail Dreazen

I. S6 Kinases	110
II. S6K Substrates and Interactors	116
III. Does S6K Regulate the Translation Efficiency of TOP mRNAs?	121
IV. Physiological Roles of S6K	135
V. Concluding Remarks	140
References	141

Regulation of Translation by Stress Granules and Processing Bodies 155

Nancy Kedersha and Paul Anderson

I. Introduction	156
II. Early History of Stress Granules	157
III. Stress Granules—Basic Attributes	165
IV. Processing Bodies/EGP Bodies/SGs in Yeast	167
V. Metazoan PBs Versus GWBs	169
VI. SG Assembly—Mechanisms and Model	170
VII. Functions and Consequences of SG/PB Assembly	172
VIII. SG/PB Dynamics	174
IX. SGs and PBs in Disease	175
X. Conclusions	179
References	179

MicroRNA-Mediated Gene Silencing 187

Cara T. Pager, Karen A. Wehner, Gabriele Fuchs,
and Peter Sarnow

I. Introduction	188
II. Biogenesis of MicroRNAs	190
III. Mechanisms of MicroRNA-Mediated Regulation	193
IV. Subversion of Liver-Specific MicroRNA <i>miR-122</i> by HCV	199
V. Antagomir Approaches to Study MicroRNA Targets	202
VI. Concluding Remarks	204
References	205

Translational Control During Early Development 211

Paul Lasko

I. Introduction	212
II. Essential Background	213
III. Translational Control Mechanisms that Pattern the Early <i>Drosophila</i> Embryo	217
IV. Cytoplasmic Regulation of Polyadenylation: A Widespread Mechanism of Translational Control Underlying Cellular Asymmetries	226
V. Polar Granules, P Granules, and Related Germline-Specific Organelles as Sites of Specialized Translation	230
VI. Translational Regulation of Maternal mRNAs Outside P Granules in <i>C. elegans</i>	233
VII. Translational Control of Localized mRNAs in the <i>Xenopus</i> Oocyte	234
VIII. Links Between Embryonic Translational Regulators and Human Disease	236
IX. Concluding Thoughts	238
References	239

The Regulation of Protein Synthesis in Cancer 255

Rafael Cuesta, Malavika Gupta, and Robert J. Schneider

I. Historical Evidence for the Role of Protein Synthesis in Cancer	256
II. Translation Initiation	256
III. The Role of eIF3 in Cancer Development	261
IV. Role of eIF2 in Cancer Development and Progression	262
V. Ribosome Biogenesis in Cancer Development	264
VI. Translational Regulation by mRNA 5'- and 3'-UTRs	267
VII. Signal Transduction Control of Translation in Cancer	273
VIII. Concluding Thoughts	280
References	281

Translational Regulatory Mechanisms in Synaptic Plasticity and Memory Storage 293

Mauro Costa-Mattioli, Nahum Sonenberg,
and Joel D. Richter

I. Synaptic Plasticity Control by eIF2	294
II. GCN2-Mediated eIF2 α Phosphorylation in Long-Lasting Synaptic Plasticity and LTM Consolidation	295

III. eIF2 α Phosphorylation and Alzheimer's Disease	297
IV. Regulation by mTOR	298
V. Regulation of Protein Synthesis-Dependent Synaptic Plasticity and Memory Consolidation by 4E-BP2 and S6K1 and S6K2	298
VI. Altered mTOR Signaling and Autism Spectrum Disorders	299
VII. FMRP and Long-Lasting Hippocampal Synaptic Plasticity	300
VIII. Translational Control by FMRP	301
IX. The Exon Junction Complex and the Regulation of Synaptic Strength	303
X. CPEB-Regulated Molecular Circuitry	304
XI. Perspective.....	306
References.....	307
 Viral Strategies to Subvert the Mammalian Translation Machinery	313
Lisa O. Roberts, Catherine L. Jopling, Richard J. Jackson, and Anne E. Willis	
I. Introduction	314
II. Viral Modification of Host Translation Machinery.....	315
III. Novel Mechanisms that Permit the Synthesis of Viral Proteins.....	336
IV. Mechanisms to Overcome Host-Mediated Translational Shut Down Caused by Phosphorylation of eIF2	347
V. General Conclusions	352
References.....	355
 RNA Aptamers to Translational Components	369
Yoshikazu Nakamura, Kei Endo, Hironori Adachi, and Akira Ishiguro	
I. Introduction	370
II. Aptamers to Translational Components.....	372
III. Other Tools for the Regulation of Translation	384
IV. Summary and Perspectives.....	386
References.....	387
Index	397