

CONTENTS

<i>Contributors</i>	<i>xiii</i>
<i>Preface</i>	<i>xvii</i>
1. Folate-Mediated One-Carbon Metabolism	1
Jennifer T. Fox and Patrick J. Stover	
I. Overview	2
II. Introduction to Cytoplasmic One-Carbon Metabolism	4
III. Introduction to Mitochondrial One-Carbon Metabolism	24
IV. Nuclear Folate-Mediated One-Carbon Metabolism	28
Acknowledgments	29
References	29
2. Mathematical Models of Folate-Mediated One-Carbon Metabolism	45
H. F. Nijhout, M. C. Reed, and C. M. Ulrich	
I. Introduction	46
II. Structure and Function of the Cycles	49
III. Why Mathematical Modeling?	51
IV. Model Development	61
V. Blood Versus Intracellular Metabolite Concentrations	66
VI. Modeling Gene–Gene and Gene–Environment Interactions	67
VII. Modeling and Simulation have Revealed Novel Homeostatic Mechanisms	70
VIII. Steady States and Fluctuations	75
IX. Conclusions	77
Acknowledgments	78
References	78
3. Folate Deprivation, the Methionine Cycle, and Alzheimer's Disease	83
Flaubert Tchanchou and Thomas B. Shea	
I. Introduction	84
II. Folate Metabolism, the Transmethylation Pathway, and AD	85
III. The Transsulfuration Pathway—Homocysteine Elimination and Glutathione Metabolism	90
References	94

4. Molecular Mechanisms of Adaptation to Folate Deficiency	99
Ilan Ifergan and Yehuda G. Assaraf	
I. Folate Metabolism	101
II. Pathological States Associated with Folate Deficiency or Nutritional Folate Insufficiency	105
III. Molecular Mechanisms of Adaptation to Folate Deprivation	108
References	131
 5. Structure and Function of the Reduced Folate Carrier: A Paradigm of a Major Facilitator Superfamily Mammalian Nutrient Transporter	 145
Larry H. Matherly and Zhanjun Hou	
I. Introduction	146
II. MFS of Transporters	147
III. Folate Transport in Tissue Folate Homeostasis and Physiology: Role of Multiple Transport Systems for Folate Uptake and Efflux	150
IV. Role of RFC in Antifolate Chemotherapy	152
V. Functional Properties of RFC	154
VI. Biochemistry of RFC	156
VII. Cloning of RFC cDNAs That Restore Transport to Transport-Impaired Cultured Cells	158
VIII. Topological Structure of RFC	159
IX. Insights into Structural and Functional Determinants of RFC from Studies of Mutant RFC Proteins	164
X. Conclusions	173
Acknowledgment	175
References	175
 6. Renal Conservation of Folates: Role of Folate Transport Proteins	 185
Vijaya L. Damaraju, Carol E. Cass, and Michael B. Sawyer	
I. Introduction	186
II. Physicochemical Properties, Protein Binding, and Water Solubility	186
III. Role of Folates in Genomic Stability	188
IV. Folates and the Kidney	188
V. Folate Transport Proteins	189
VI. Localization of Putative Folate Transporters in Kidney	192
VII. Clinical Studies of Renal Handling of Folates and Antifolates	193
VIII. Role of Renal Folate Conservation in Ethanol-Related Folate Deficiency	196
IX. Role of Folate Transport Processes in Renal Conservation of Folates and Antifolates	197
References	198

7. Exploitation of the Folate Receptor in the Management of Cancer and Inflammatory Disease	203
Christopher P. Leamon and Ann L. Jackman	
I. Introduction	204
II. Aspects of the FR	205
III. Exploitation of the FR for Disease Management	208
IV. Future Prospects	225
References	226
8. Folate Receptor Expression in Pituitary Adenomas: Cellular and Molecular Analysis	235
Chheng-Orn Evans, Congjun Yao, David LaBorde, and Nelson M. Oyesiku	
I. Introduction	236
II. Methods	238
III. Result	242
IV. Discussion	259
Acknowledgments	263
References	263
9. Regulation of Human Dihydrofolate Reductase Activity and Expression	267
Emine Ercikan Abalı, Nancy E. Skacel, Hilal Celikkaya, and Yi-Ching Hsieh	
I. Introduction	268
II. Structure and Binding of Dihydrofolate, MTX, and NADPH	269
III. Mechanism of DHFR Catalysis	272
IV. Alternative Substrates: Folic Acid and Dihydrobiopterin	273
V. Genomic Organization of DHFR	274
VI. Human Dihydrofolate Reductase Pseudogenes	276
VII. Transcriptional Regulation	276
VIII. Polymorphisms of DHFR	280
IX. Posttranscriptional Regulation of DHFR	283
X. Translational Regulation of DHFR	283
Acknowledgments	287
References	287
10. Catalysis of Methyl Group Transfers Involving Tetrahydrofolate and B₁₂	293
Stephen W. Ragsdale	
I. Introduction to Methyltransferases and Their Cofactors	294
II. Three Component Systems Required for B ₁₂ /THF-Dependent Methyltransferases	296

III. Biological Systems Impacted by B ₁₂ and Folate-Dependent Methyltransferases	297
IV. Structure and Function of B ₁₂ in Methyltransferases	301
V. Activation of the Methyl Group Donors	307
VI. Activation of the Methyl Group Acceptors: Zn Thiolates and NiFeS Clusters	314
Acknowledgments	317
References	317
11. Methyltetrahydrofolate in Folate-Binding Protein Glycine N-Methyltransferase	325
Zigmund Luka	
I. Introduction	326
II. 5-Methyltetrahydrofolate in Folate Metabolism	326
III. Folate-Binding Enzymes	330
IV. Glycine N-Methyltransferase	331
V. GNMT as Methyltetrahydrofolate-Binding Protein	335
VI. Conclusions	340
Acknowledgments	341
References	341
12. Mechanism-Based Inhibitors of Folylpoly-γ-Glutamate Synthetase and γ-Glutamyl Hydrolase: Control of Folylpoly-γ-Glutamate Homeostasis as a Drug Target	347
James K. Coward and John J. McGuire	
I. Introduction	348
II. Folylpoly- γ -Glutamate Homeostasis as a Drug Target	350
III. Design of Fluoroglutamate-Containing Folates and Antifolates as FPGS or GH Alternate Substrates and/or Inhibitors	354
IV. Synthesis of Fluorine-Containing Folates and Antifolates from the Corresponding Fluoroglutamates and Related Fluoroamino Acids	356
V. Design of Phosphorus-Containing Pseudopeptides as FPGS Inhibitors	361
VI. Design of Epoxide-Containing Peptidomimetics as GH Inhibitors	366
VII. Conclusions	366
Acknowledgment	367
References	367
13. Methylene tetrahydrofolate Reductase, Common Polymorphisms, and Relation to Disease	375
Philip Thomas and Michael Fenech	
I. Introduction	376
II. Conclusions	386
References	386

14. Mitochondrial Methylenetetrahydrofolate Dehydrogenase, Methenyltetrahydrofolate Cyclohydrolase, and Formyltetrahydrofolate Synthetases	393
Karen E. Christensen and Robert E. MacKenzie	
I. Introduction	394
II. Yeast Mitochondria Contain a Trifunctional Dehydrogenase–Cyclohydrolase–Synthetase	395
III. Mammalian Mitochondrial Methylenetetrahydrofolate Dehydrogenase	395
IV. Mitochondrial Formyltetrahydrofolate Synthetase	403
V. Conclusion	405
References	408
 15. The Structure and Mechanism of 6-Hydroxymethyl-7,8-Dihydropterin Pyrophosphokinase	 411
Jeremy P. Derrick	
I. Introduction	412
II. Structural and Mechanistic Studies on EcoHPPK	413
III. Structures of HPPKs from Other Organisms	421
IV. Kinetics	424
V. Relationship of HPPK to Other Pyrophosphoryl Transfer Enzymes	426
VI. Concluding Remarks	429
References	430
 <i>Index</i>	 435