

CONTENTS

INTRODUCTION	xiii
LIST OF CONTRIBUTORS	xxiii
 PART I ASSESSING TRANSMEMBRANE MOVEMENT AND ASYMMETRY OF LIPIDS	 1
1 Methods for the Determination of Lipid Transmembrane Distribution and Movement in Biological Membranes	3
<i>Philippe F. Devaux and Andreas Herrmann</i>	
1.1 Introduction, 3	
1.2 Development of Assays for Distribution and Translocation of Lipids across Membranes, 4	
1.3 Overview on Assays for Measuring Distribution and Translocation of Lipids across Cellular Membranes, 7	
1.4 Main Techniques Used to Determine Transbilayer Distribution of Endogenous Lipids in Cell Membranes, 9	
1.5 Main Techniques Used to Determine Transbilayer Distribution of Lipid Analogs in Cell Membranes, 12	
Abbreviations, 21	
References, 21	
 2 Detection and Measurement of Unlabeled Lipid Transmembrane Movement	 25
<i>Iván López-Montero, Marisela Vélez, and Philippe F. Devaux</i>	
2.1 Introduction, 25	
2.2 Measurement of Transmembrane Flip-Flop of Unlabeled Lipids by Shape Change of GUVs, 27	

- 2.3 Measurement of Transmembrane Flip-Flop of Unlabeled Lipids Using AFM, 36
- 2.4 Conclusions, 41
- Acknowledgments, 41
- Abbreviations, 41
- References, 42

PART II LIPID ASYMMETRY IN CELL MEMBRANES 45

3 New Insights in Membrane Lipid Asymmetry in Animal and Plant Cells 47

Alain Zachowski

- 3.1 Lipid Asymmetry in Animal Membranes, 47
- 3.2 Creating, Maintaining, or Randomizing the Membrane Phospholipid Distribution: Phospholipid Transporters, 49
- 3.3 What about Lipid Asymmetry and Translocation in Plant Cell Membranes?, 50
- Abbreviations, 61
- References, 61

4 Sphingolipid Asymmetry and Transmembrane Translocation in Mammalian Cells 65

Gerrit van Meer, Sylvia Neumann, and Per Haberkant

- 4.1 Introduction, 65
- 4.2 Sphingosine, Sphingosine-1-Phosphate, and Ceramide, 67
- 4.3 Ceramide, 68
- 4.4 Glycosphingolipids, 68
- 4.5 Sphingomyelin, 70
- 4.6 Future Perspectives, 71
- Abbreviations, 71
- References, 71

5 Transbilayer Movement and Distribution of Cholesterol 75

Peter Müller, Anna Pia Plazzo, and Andreas Herrmann

- 5.1 Introduction, 75
- 5.2 Physicochemical Features of Cholesterol, 76
- 5.3 Methods for Measuring Cholesterol Transbilayer Movement and Distribution, 77
- 5.4 Transbilayer Movement of Cholesterol in Model Membranes, 81
- 5.5 Transbilayer Movement of Cholesterol in Biological Membranes, 82

5.6	Transbilayer Distribution of Cholesterol in Lipid and Biological Membranes, 82
5.7	Cholesterol Flip-Flop: Fast or Slow?, 87
5.8	Role of Proteins in the Transport of Cholesterol across Membranes, 88
5.9	Concluding Remarks, 90
	Acknowledgment, 92
	Abbreviations, 92
	References, 93

PART III ENERGY-INDEPENDENT PROTEIN-MEDIATED TRANSMEMBRANE MOVEMENT OF LIPIDS **97**

6 Phospholipid Flip-Flop in Biogenic Membranes **99**

Anant K. Menon and Andreas Herrmann

6.1	Introduction, 99
6.2	Assays for Measuring Transbilayer Distribution of Endogenous Phospholipids, 100
6.3	Assays for Measuring Transbilayer Distribution and Movement of Phospholipid Analogs, 102
6.4	Shape Changes of GUVs as a Tool to Measure Flip-Flop, 106
6.5	Transbilayer Movement of Phospholipids in the ER, 108
6.6	Transbilayer Movement of Phospholipids in the Bacterial Inner Membrane, 110
6.7	Mechanism of Rapid Lipid Flip-Flop in Biogenic Membranes, 112
6.8	Efforts to Identify Phospholipid Flippases, 113
6.9	Flipping of Isoprenoid-Based Glycolipids, 115
6.10	Conclusion, 115
	Abbreviations, 116
	References, 116

7 Phospholipid Scramblase: When Phospholipid Asymmetry Goes Away **119**

Edouard M. Bevers and Patrick L. Williamson

7.1	Introduction, 119
7.2	Historical Overview, 120
7.3	Physiological Importance of Lipid Scrambling, 122
7.4	Characteristics of the Phospholipid Scrambling Process, 124
7.5	Toward Identification: Proposed Candidate Proteins and Mechanisms, 132
7.6	Concluding Remarks, 139
	Abbreviations, 139
	References, 140

PART IV ENERGY-DEPENDENT LIPID TRANSPORT ACROSS MEMBRANES	147
8 Flip or Flop: Mechanism and (Patho)Physiology of P₄-ATPase-Catalyzed Lipid Transport	149
<i>Patricia M. Verhulst, Joost C.M. Holthuis, and Thomas G. Pomorski</i>	
8.1 Introduction, 149	
8.2 P ₄ -ATPases are Prime Candidate Phospholipid Translocases, 152	
8.3 Mechanism of P ₄ -ATPase-Catalyzed Lipid Transport: Role of Accessory Subunits, 156	
8.4 Role of P ₄ -ATPases in Vesicle-Mediated Protein Transport, 161	
8.5 P ₄ -ATPase Dysfunction and Disease, 162	
8.6 Future Challenges, 166	
Acknowledgments, 166	
Abbreviations, 166	
References, 167	
9 Coupling Drs2p to Phospholipid Translocation, Membrane Asymmetry, and Vesicle Budding	171
<i>Xiaoming Zhou, Paramasivam Natarajan, Baby-Periyannayagi Muthusamy, Todd R. Graham, and Ke Liu</i>	
9.1 Introduction, 171	
9.2 P ₄ -ATPases in Budding Yeast, 172	
9.3 Evidence That Drs2p Is a Flippase, 175	
9.4 Drs2p in Protein Transport and Vesicle Budding, 183	
9.5 Concluding Remarks, 191	
Abbreviations, 192	
References, 193	
10 Substrate Specificity of the Aminophospholipid Flippase	199
<i>Shelley M. Cook and David L. Daleke</i>	
10.1 Introduction, 199	
10.2 Substrate Specificity of the PM Aminophospholipid Flippase, 200	
10.3 Identification and Substrate Specificity of Candidate Aminophospholipid Flippases, 205	
10.4 Is the Lipid Specificity of Candidate Aminophospholipid Flippases Unique?, 210	
10.5 Lipid Specificity of Other PS-Binding Proteins, 213	
10.6 Sequence Elements That Bind to PS, 215	
10.7 Conclusions, 216	
Acknowledgments, 217	
Abbreviations, 218	
References, 218	

11 The Flippase Delusion? 225*Naomi L. Pollock, Petra H.M. Niesten, and Richard Callaghan*

- 11.1 ATP-Binding Cassette (ABC) Transporters and Lipid Flip-Flop, 225
- 11.2 ABCA4 and Lipid Translocation: Explaining a Phenotype?, 228
- 11.3 MsbA and Lipid Translocation: A Key to Survival, 230
- 11.4 Drug and Lipid Movement by ABCB1: Is the Mechanism a Flip-Flop?, 237
- 11.5 ABCB4: The Forgotten and Likely Lipid Flippase?, 240
- 11.6 Conclusions and Perspectives, 244
- Abbreviations, 244
- References, 245

PART V RELEVANCE OF LIPID TRANSMEMBRANE DISTRIBUTION FOR MEMBRANE PROPERTIES AND PROCESSES 251**12 Membrane Lipid Asymmetry and Permeability to Drugs: A Matter of Size 253***Adam Blanchard and Cyril Rauch*

- 12.1 Introduction, 253
- 12.2 The Origin of Lipinski's Second Rule from the Point of View of the Pharmaceutical Industry, 254
- 12.3 Solving Lipinski's Second Rule, 257
- 12.4 Lipinski's Second Law and Potential Application, 264
- 12.5 Conclusion, 270
- Acknowledgment, 272
- Abbreviations, 272
- References, 273

13 Endocytosis and Lipid Asymmetry 275*Nina Ohlwein, Andreas Herrmann, and Philippe F. Devaux*

- 13.1 Introduction, 275
- 13.2 Bending a Membrane, 276
- 13.3 Shape Changes of GUVs Induced by Lipid Asymmetry, 278
- 13.4 How Endocytosis Is Linked to Lipid Asymmetry, 280
- 13.5 Role of P₄-ATPases in the Formation of Endocytic Invaginations, 283
- 13.6 Concluding Remarks, 284
- Acknowledgments, 285
- Abbreviations, 285
- References, 285

PART VI APOPTOSIS AND DISEASES: CONSEQUENCES OF DISRUPTION TO LIPID TRANSMEMBRANE ASYMMETRY	289
14 Membrane Lipid Asymmetry in Aging and Apoptosis	291
<i>Krishnakumar Balasubramanian and Alan J. Schroit</i>	
14.1 Introduction, 291	
14.2 Phospholipid Transporters, 292	
14.3 Lipid Asymmetry in Erythrocytes, 294	
14.4 Lipid Asymmetry during Apoptosis, 297	
14.5 Ca^{2+} Homeostasis during Apoptosis, 298	
14.6 Membrane Phospholipid Asymmetry: Static or Dynamic?, 299	
14.7 Regulation of Lipid Asymmetry during Apoptosis, 300	
14.8 Significance, 304	
14.9 Concluding Remarks, 306	
Abbreviations, 306	
References, 307	
15 Phosphatidylserine Exposure in Hemoglobinopathies	315
<i>Frans A. Kuypers and Eric Soupene</i>	
15.1 Introduction, 315	
15.2 RBC Phospholipid Organization, 316	
15.3 The RBC Flippase, 319	
15.4 PS Exposure in RBCs, 324	
15.5 PS Exposure in Hemoglobinopathies, 328	
15.6 Consequences of PS Exposure, 329	
15.7 Phospholipid Transbilayer Movement in Hemoglobinopathies, 330	
15.8 Conclusion, 332	
Abbreviations, 333	
References, 334	
16 Scott Syndrome: More Than a Hereditary Defect of Plasma Membrane Remodeling	341
<i>Florence Toti and Jean-Marie Freyssinet</i>	
16.1 Introduction, 341	
16.2 Scott Syndrome Features and Phenotype, 342	
16.3 Cell Biology of Scott Syndrome, 343	
16.4 Candidate Proteins in the Transmembrane Redistribution of PS, 345	
16.5 The Significance of Membrane Vesiculation and of Derived MPs, 346	
16.6 What Can Be Learned from Scott Syndrome?, 347	

- 16.7 Conclusion, 348
- Abbreviations, 349
- References, 350

17 ABCA1, Tangier Disease, and Lipid Flopping

353

Ana Zarubica and Giovanna Chimini

- 17.1 Historical Notes: Tangier Disease (TD) and ATP-Binding Cassette Transporter 1 (ABCA1), 353
- 17.2 The ABCA1 Gene and the Regulation of Its Expression, 354
- 17.3 The ABCA1 Protein and Its Interactions, 356
- 17.4 ABCA1: Mutations and Clinical Signs, 358
- 17.5 Targeted Inactivation and Overexpression of ABCA1 in Animal Models, 360
- 17.6 Liver and Macrophage ABCA1: Lipid Efflux and HDL Formation, 362
- 17.7 ABCA1 and Membrane Function, 363
- 17.8 ABCA1: Lipid Flop and Lipid Efflux, 364
- 17.9 ABCA1 and the Lipid Microenvironment at the Membrane, 366
- 17.10 Conclusions, 368
- Acknowledgments, 369
- Abbreviations, 369
- References, 371

INDEX

379

Note: Color versions of many of the black and white figures in this book can be viewed at ftp://ftp.wiley.com/public/sci_tech_med/transmembrane_dynamics. Please read the figure captions to learn which figures are available on the ftp site.